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Venous occlusion plethysmography in 55-year old men

A population study in Malmö, Sweden

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SVEN-OLOF ISACSSON

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A POPULATION STUDY IN MALMÖ, SWEDEN

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1. INTRODUCTION

Arteriosclerosis with its complications is a predominant cause of incapacity and death in developed countries. Against this background, intensive research on the epidemiology of cardiovascular diseases has been carried out during the last two decades. Many longitudinal studies have been performed, perhaps the best known being the Framingham (Dawber *et al.* 1951) and Tecumseh studies (Epstein 1960).

At an early stage, the cardiovascular section of the World Health Organization (WHO) showed an interest in epidemiological investigations of arteriosclerosis as well as of other cardiovascular diseases (WHO Chronicle 1965). Therefore, the cardiovascular diseases have become international concerns and WHO has played an important co-ordinating rôle in the accomplishment of studies in different member states (Keys *et al.* 1967).

Arteriosclerosis can be regarded as a systemic disease, but with predilections for three vascular regions. These predilections are for the coronary arteries, the cerebral arteries, and the femoral arteries. Furthermore, the degree of arteriosclerosis may vary considerably from one vascular region to another. This has been clearly shown in the extensive autopsy study by Sternby (1968).

Modern computer technique has made it possible to evaluate many factors and their interrelations which are pertinent to the epidemiological study of arteriosclerotic diseases. Coronary artery disease has thus been subjected

to the most intensified study. The factors found to have the strongest correlation to coronary artery disease are smoking, hypercholesterolaemia, hypertension, and lack of physical activity. These factors are generally called *risk factors*, which means that a statistical correlation has been demonstrated between these factors and coronary artery disease.

Obesity was also considered an important risk factor in coronary artery disease, but later research suggests that this condition is probably less important than the others previously mentioned (Keys 1970).

Other risk factors have also been found, but they have been either very little studied or proved to have a weaker relation to coronary artery disease. Nonetheless, some of these are worth mentioning and include electrocardiographic abnormalities, personality variables, heredity, diabetes mellitus, hypertriglyceridaemia, lipoprotein electrophoretic abnormalities, high haemoglobin concentration and hyperuricaemia. Thorough reviews of the vast literature in this field were provided by Epstein (1965) and Simborg (1970). Later investigations have shown that high resting heart rate also is an important risk factor (Berkson *et al.* 1970).

Even though the interest in earlier epidemiological studies was focused mainly on coronary artery disease, considerable interest has recently been demonstrated in the epidemiology of cerebrovascular diseases (Kuller *et al.* 1969, Dawber and Thomas 1969). The Framingham

study (Dawber and Thomas 1969) showed that hypertension, hypercholesterolaemia, diabetes mellitus, smoking, obesity, and high haemoglobin concentration were risk factors for cerebrovascular disease (stroke). Several of the risk factors consequently are important in both coronary and cerebrovascular disease. However, this does not eliminate the possibility that the individual risk factors might be more strongly related to one of these diseases than to the other. Several investigations, most notably those by Bjurulf (1964) and Sternby (1968) disclosed a much stronger correlation between hypertension and arteriosclerosis of the cerebral vessels than between hypertension and arteriosclerosis of the coronary vessels.

During the 15 last years, interest in the epidemiology of cardiovascular diseases has increased strikingly in Sweden (Forssman and Lindegård 1958, Nilsson *et al.* 1964, Biörck 1965, Tibblin *et al.* 1965, Carlson and Lindstedt 1968, Furberg *et al.* 1972) and also in many other countries. In Sweden, the cardiovascular diseases represent an important cause of early incapacity and death, not only among the aged but also in the middle-aged working population. About one half of all deaths of those in their productive years are caused by these diseases (Werkö 1969). Arteriosclerosis is the foremost of the cardiovascular diseases.

Population studies have been carried out in Gothenburg of both men and women (Tibblin *et al.* 1965, Tibblin 1969) and the incidence of myocardial infarction and stroke has been studied with the aid of special infarction (WHO 1969, 1970) and stroke (WHO 1971) registers, as recommended by WHO. Furthermore, a vast study is in progress, primarily preventive in nature, which will examine the dangers of combinations of risk factors (Wilhelmsen *et al.* 1971).

The results of the present study are based on an investigation carried out in Malmö, where the interest in the epidemiology of cardiovascular diseases has been very great for more than a decade (Biörck *et al.* 1957). Autopsy studies

of myocardial infarctions in Malmö during the years 1954–1959 have been reported by Söderström (1961). Bjurulf (1964) focused his interest on atherosclerosis in different parts of the arterial system. Sternby (1968) studied the frequency of occurrence of atherosclerosis in a defined population. Bjurulf *et al.* (1967) evaluated cardiovascular symptoms and ECG-findings and related these to carefully performed autopsy examinations with special attention to the coronary arteries and the heart. Also a comparison of blood pressure taken under casual and basal conditions as related to the degree of arteriosclerosis was carried out by Bjurulf and Sternby (to be published).

The Malmö studies, referred to above, illustrate the extent of local interest in the epidemiology of cardiovascular diseases and provide a precedent from which to launch further research in this field. The present work was designed as a clinical-pathological study, the first aspect of which was a cross-sectional investigation of randomly selected men. Clinical follow-up studies were planned and, after death, every subject was to undergo a special autopsy of the vascular system (cerebral vessels, coronary vessels, aortic parts, and leg arteries from the hip to the ankle with preservation of these blood vessels in formaldehyde sacks). In this situation, a comparison would be possible between data collected earlier in connection with the clinical study and the pathologic-anatomical appearance of the arterial system.

Manifestations of disease from two of the three favoured locations for arteriosclerosis (the coronary arteries and the cerebral arteries) have been studied epidemiologically. The interest in the third place of predilection (femoral arteries) has been smaller. It therefore seems appropriate to cite G. Schettler's introductory speech at the Second International Symposium on Atherosclerosis: "What are the problems we should deal with in the future? As a clinician I would like to mention a few points. Epidemiology should focus not only on coronary heart disease but also on other vascular areas and

should use all available diagnostic tools. The risk factors in atherogenesis will have different weights in different vascular areas." (Schettler 1970). Technically, it is easier to study the circulation in the legs than to study the coronary or the cerebral circulation. In connection with an epidemiological investigation regarding heart diseases, vascular diseases, and lung diseases in 55-year-old men, it was considered important to direct some attention to the peripheral arterial tree as well.

No studies are available in the existing literature which describe attempts at objective measurements of the leg blood flow in a randomly selected material. In the previously mentioned epidemiological investigations, the methods for examining the circulation of the legs has been medical history and pulse palpation. Because of this, intermittent claudication has sometimes become a diagnosis synonymous with arterial obliteration (Fodor *et al.* 1968).

However, medical history and pulse palpation have proved to be poor methods for surveying the prevalence of femoral stenoses or occlusions in a large population. This has been shown in several reports by Widmer and his co-workers (1963, 1967 and 1970). With a special method of investigation including not only medical history, but pulse palpation, oscillometry, and auscultation before and after leg exercise, Widmer examined a large number of men and women employed by the Swiss pharmaceutical factories in Basel. In this selected material, he was able to verify a preliminary diagnosis of femoral artery disease angiographically in 90 % of the cases detected with the described methods. He observed that stenoses or occlusions in the

femoral arteries existed in 1 % of the men aged 40–50 and increased successively by year to about 7 % in men aged 65–74. Higher incidence has been reported in hospital patients (Marti 1961). Widmer also analysed the relation between risk factors in cardiovascular disease and coexisting stenosis and occlusion in the femoral arteries (Widmer *et al.* 1969). He was able to demonstrate that systolic hypertension, heavy cigarette smoking, and increased beta-lipoproteins in serum were more common in individuals with occlusions of the arteries of the legs than in individuals without arterial diseases. But there were no differences in cholesterol level or obesity between persons with and without arterial diseases.

It is much easier to measure quantitatively the blood flow in the leg arteries than in other vascular regions, such as coronary arteries or cerebral arteries. In the present study, venous occlusion plethysmography was used in order to objectively measure the arterial flow capacity of the legs. The objectives were:

(1) to evaluate the utility of venous occlusion plethysmography as a method of epidemiologic investigation;

(2) to validate the diagnosis of intermittent claudication established with the aid of a cardiovascular questionnaire (Rose and Blackburn 1968) against the results of venous occlusion plethysmography;

(3) to compare the results of venous occlusion plethysmography with other data gathered in connection with the population study (medical history, clinical findings, laboratory data).

The investigation is a cross-sectional study. Follow-up studies are planned.

2. DESCRIPTION OF THE STUDIED POPULATION

Demographic and geographic data

Based on its number of inhabitants, Malmö is the third largest city in Sweden. It is situated on the far south-west coast. The climate is relatively mild by Swedish standards, the coldest month being February, average temperature -0.7°C . July is the warmest month, average temperature $+17.3^{\circ}\text{C}$; it also has the greatest precipitation (average 65 mm), and March the lowest (30 mm).

The census reported on December 31, 1969 revealed that Malmö had 258,311 inhabitants: 125,058 men and 133,253 women. The same census showed that the inhabitants of Malmö represented 3.22 % of the total population of Sweden (Statistisk Årsbok, Malmö, 1970). There is a relative equilibrium between the number of people moving in and out of the city. In 1967 and 1968, respectively, approximately 11,000 persons moved into the city and about the same number moved out.

There are three hospitals in Malmö. The main hospital, *Malmö General Hospital*, is a university hospital and is well represented in the various medical specialities. *Värnhem's Hospital* is a hospital for chronic diseases and *Malmö Östra Hospital* is a mental hospital.

The pathology department of Malmö General Hospital provides service for the entire city. In 1969 the post-mortem examination rate was 91 %. Between 1965 and 1969 autopsies were performed on 92 % of the 75 males who died in their fifty-fifth year (Sternby, personal communications).

The studied population

The population was selected with the aid of the County Council in Malmö, which is obliged to keep reliable and current statistics regarding the inhabitants of the city. The group consisted of all men born in an even-numbered month in 1914 (*i.e.* February, April, June, August, October, and December), and residing in Malmö at the time of the investigation.

The Malmö investigation chose men aged 55 in order to make a comparison with a Gothenburg study, where men born in 1913 were examined in 1963 and again in 1967 when they were 54 years old (Tibblin 1970).

The total group consisted of 809 men when selection was terminated in November 1968. They were requested to participate in a combined health examination and population study on a specified date. Information about those men who were not able to be present at the examination was collected to the greatest possible extent through letter-questionnaires, telephone interviews, hospital dossiers, and visits.

The studied population is presented in Table 1. Of the 809 persons summoned, 703 (87 %) appeared at the routine examinations presented in Table 3 in the next chapter. The examinations were carried out at the Department of Clinical Physiology, Värnhem's Hospital. Useful information was obtained from another 64 persons. Of the original population, 42 men (5 %) were not included in any kind of interview or examination. Table 2 shows a comparison of the

Table 1. Extent of participation of 809 men in Malmö born 1914.

	n	%
Selected material	809	100
Full participation in the population study	703	86.9
Limited participation (home visits, interviewed by telephone, hospital dossiers)	64	7.9
Non-participants	42	5.2

group who took part in the scheduled examination with the 64 persons who were surveyed in another ways.

Definitions of the diagnoses provided in Table 2 are presented in the next chapter. Of the group, 13 were invalid pensioners; 12 of them took part in the population study. They were pensioned on account of psychic or somatic disease leading to total incapacity for work. Only one of the 12 was retired because of cardiovascular disease.

Eighteen of the 809 men were of foreign extraction but had resided in Malmö for many years; they did not differ from the rest of the population concerning leg blood flow.

DISCUSSION

Generally speaking the degree of arteriosclerosis is higher in males than in females aged below 70 in all parts of the arterial system with the

exception of the cerebral arteries, where sex and age variations are not so marked (Sternby 1968). It is therefore important to isolate the effects of sex and age when applying epidemiology to the study of arteriosclerosis.

Differences due to sex and age had no influence on the results of this study, because the material was age- and sex-specific.

The individuals were contacted by telephone a few days before the decided date for the examinations. At that time, an effort was made to persuade them to participate in the study. In this manner, it was usually possible to examine the individuals within or quite close to their birth month. In effect, this practice resulted in the structure of a population with a mean age of 55 years ± 1 month.

The results derived from this population study would not have been valid if the number of participants had been too small. There is a great risk that the individuals who do not appear at the examination form a special group differing in some consistent way from the rest of the material.

The 1963 Gothenburg population study was of men born in 1913 (Tibblin *et al.* 1965, Tibblin 1967); 88 % of the 973 selected (hospital group) attended the preliminary examination. Four per cent were examined at home. Eight per cent did not take part. A comparison between the hospital examined group, the home-group and the non-participant group (Tibblin 1966) revealed that

Table 2. Comparison between full and limited participation.

	Full participation n=703 (86.9 %)		Limited participation n=64 (7.9 %)	
	n	%	n	%
Previously hospitalized (any reason)	449	63.9	37	57.8
Previously hospitalized (because of myocardial infarction)	10	1.4	0	0
Angina pectoris (questionnaire)	42	6.0	3	4.7
Intermittent claudication (questionnaire)	20	2.8	2	3.1
Diabetes mellitus	12	1.7	2	3.1
Cancer	8	1.1	1	1.5
Chronic bronchitis (questionnaire)	47	6.7	5	7.8
Smokers	436	62.0	35	55.0
Invalid pensioners	12	1.7	1	1.5

the latter differed from the other groups socio-economically. Those who failed to take part had a lower average annual income and evidenced alcoholism to a larger extent than the other groups. The percentage of men who did not appear at the examination in the present study agrees almost exactly with that reported in Gothenburg. No exact survey of the socio-economic differences between those who took part and those who did not take part in this investigation has been performed. Judging from the Gothenburg-results we may postulate that such differences existed also in this population.

The 42 persons who took no part whatever in the present investigations had, on the average, been previously hospitalized to the same extent as the other subjects, but had been sick-reported a little more often.

The purpose of the present report is among other things to relate calf blood flow to the prevalence of intermittent claudication, myocardial infarction, and diabetes mellitus. The prevalence of these symptoms and diseases was essentially the same in those who were examined and in the 64 persons from whom information was gathered in other ways. There was no difference between their smoking habits, a fact of great importance in the present study.

Useful information has been obtained regarding approximately 95 % of the selected material. Even if certain socio-economical differences may have existed between members of the examined group and those individuals who did not take part in the examination, the 87 % who came to the examinations were considered representative of 55-year-old men.

3. METHODS AND DEFINITIONS

METHODS

This chapter provides a description of the methods applied to the *population study*.

A thorough *follow-up study of the peripheral circulation* was carried out on subgroups selected from the original material, and the methods applied to this study will also be described.

Procedure of investigation

Four individuals were examined every weekday from January 1969 through January 1970. In Sweden, July is the most common holiday month; thus no examinations were carried out between June 25 and August 8, 1969. The subjects had been asked to fast from food, drink, and tobacco beginning at midnight before the examination, which began at 7:30 a.m. (see Table 3).

Examinations were initiated by general information for 10 to 15 minutes, while the

subject was resting in sitting position. The sitting blood pressure, the weight, and the standing height were measured, and then the subject continued to the next station, where ECG was recorded. Lung function was examined, followed by sampling sputum for cytology and venous occlusion plethysmography. Heart and lungs were X-rayed. After a light meal, the subjects were interviewed and examined. The physical examination comprised auscultation of the heart and lungs, palpation of peripheral pulses, abdominal status, and rectal examination. In most cases, the entire examination was completed by approximately 11:30 a.m.

Questionnaire

The questionnaire which was used in order to obtain the personal and family medical histories — including smoking habits, bronchial symptoms, physical activity, and stress—also solicited information about cardiovascular symptoms. The *cardiovascular questionnaire* was originally composed by a WHO committee and was then validated at the London School of Hygiene and Tropical Medicine (Rose 1962, Rose and Blackburn 1968). A Swedish translation was used in this present investigation. The questionnaire was the same as that used in the population study in Gothenburg of men born in 1913 (Tibblin *et al.* 1965).

The subjects were assigned to one of three groups according to their *smoking habits*: (1) those who had *never smoked* (criterion: less

Table 3. Routine examinations.

Blood pressure (sitting)
Blood tests (cholesterol, triglycerides, haematocrit)
Height
Weight
ECG
Lung function (spirometry, nitrogen wash-out)
Sputum cytology
Heart-lung X-ray
Calf blood flow (venous occlusion plethysmography)
Interview (questionnaire)
Physical status (examination)

than one cigarette per day for less than a year); (2) *ex-smokers*, comprising individuals who had stopped smoking at least one month before this investigation after having smoked regularly; and (3) *smokers*. This latter group was sub-divided into inhalers and non-inhalers. Tobacco consumption was quantified as follows:

1 cigarette=1 gm tobacco, 1 cigarillo=2 gm, 1 cigar=5 gm.

Pipe tobacco consumption and the approximate total amount of tobacco consumed was given in gm/day. On these bases, the smokers were then assigned to one of three groups corresponding to a daily consumption of 1–14 gm, 15–24 gm or 25 gm and more.

One year after the survey, 100 of the previously examined individuals were randomly selected and interviewed again regarding their smoking habits. These new responses and the original ones were almost identical in 90 % of the cases with the greatest changes being no more than about ± 2 gm. Changes in tobacco consumption greater than 5 gm were evident in only 2 % of the cases.

A careful history of *physical activities* was taken for each participant. Subsequently, subjects were grouped according to *spare-time* and

occupational activity as described by Wilhelmsen (1969).

In order to quantify the occupational activity, every individual was requested to describe the different kinds of work he did during a typical work day. The lifting and carrying of heavy objects (10–20 kg and more) were noted as were sitting and moving times. Spare-time activities included method of transport to and from work and were tabulated in the same way. Occupation during evenings and days off was noted. Participation in sport activities and the duration and intensity of such participation was also recorded. Once acquired, this information made it possible to divide the material into four groups according to spare-time, and occupational activities (Table 4). The amount of physical activity during the following periods of life was recorded for each subject: age 20–29, 30–39, 40–49, 50–54, and during the last year.

A rough estimate of the occurrence of *psychic stress* was obtained with the aid of a combination of questions (Wilhelmsen 1969). The subjects were asked whether they were troubled by such things as uneasiness, nervousness, and anxiety and whether these were associated with economic problems, family problems, disease or problems

Table 4. Group assignment according to occupational physical activity (A) and spare-time physical activity (B) (according to Wilhelmsen, 1969).

A. Occupational physical activity			
Group I	Group II	Group III	Group IV
Predominantly sedentary, sitting: desk worker, watch maker, sitting assembly-line worker (light goods) etc.	Sitting or standing, some walking: cashier, general office worker, light tool and machinery worker, foreman, etc.	Walking, some handling of material: mailman, waiter, construction worker, heavy tool and machinery worker, etc.	Heavy manual work: lumberjack, dock worker, stone mason, farm worker, ditch digger, etc.
B. Spare-time physical activity			
Group I	Group II	Group III	Group IV
Almost completely inactive: reading, TV watching, movies, etc.	Some physical activity during at least 4 hours per week: riding a bicycle or walking to work, walking or skiing with the family, gardening, etc.	Regular activity: such as heavy gardening, running, calisthenics, tennis, etc.	Regular hard physical training for competition in running events, soccer, racing, European handball, etc., several times per week

at work. The participants, according to their responses, were assigned to six groups, corresponding to increasing psychic stress. Group I comprised individuals who could recall no periods of stress, and group VI of individuals who claimed to have had continuous stress during the past five years.

Blood pressure measurements

The recommendations from WHO were followed (Rose and Blackburn 1968). All blood pressure measurements were made by the author with the subjects in the sitting position. The mercury manometer was used throughout. Measurements were made in the mornings between 7:45 and 8:15. The room temperature was kept constant during the year at 23–24°C. After 10–15 minutes spent on routine information while the subject was seated, a blood pressure cuff with a rubber bladder 12 cm wide and 26 cm long was placed on the right arm. Systolic and diastolic blood pressures were recorded to the nearest 5 mm Hg. The systolic blood pressure was noted as the pressure read on the manometer at the auscultation of the first sound, and the diastolic (phase 5) recorded as the observed pressure when the sound had disappeared entirely.

Pulse palpation

Bilateral simultaneous pulse palpation was done routinely at the carotid, femoral, posterior tibial, and the dorsalis pedis arteries. The results were recorded only as positive or negative.

Height and weight

Height and weight were determined according to the recommendations of WHO (Rose and Blackburn 1968). The subjects were examined while unclothed except for undershorts.

The weight was determined to the closest 0.1 kg with a lever balance.

The height was measured to the nearest 0.5 cm while the subjects were without shoes and with their heels, hips, shoulders, and backs of their

heads in contact with the wall and eyes looking straight ahead.

Electrocardiographic examination

Electrocardiograms were made by a skilled laboratory assistant while the subject was recumbent and had been so positioned for about 5 minutes. A direct-writing recorder (Mingograph 42 B, Elema-Schönander AB, Sweden) was used and four leads were recorded simultaneously. The paper speed was 50 mm/sec. Leads I, II, III, aVR, aVL, aVF, V₁, V₂, V₃, V₄, V₅, and V₇ were recorded. The electrocardiograms were interpreted according to the Minnesota code (Blackburn *et al.* 1960) and always by the same skilled researcher,¹ who had no information about the individual. A random selection of these records were examined by a second interpreter who was employed by WHO. Comparison of both sets of interpretations revealed 94 % agreement.

Heart volume

The heart volume was determined with the subjects standing, according to the method described by Jonsell (1939). The X-ray pictures were inspected by an experienced roentgenologist² who had no other information regarding the individuals. Absolute and relative heart volumes were given in ml. The relative heart volume was given in ml/m² body surface area.

Venous occlusion plethysmography

The calf blood flow at rest and also during reactive hyperaemia was determined with venous occlusion plethysmography. A water-filled plethysmograph was used and the apparatus and technique were essentially those of Dahn (1965).

The plethysmographic examination was performed on both legs simultaneously with the subject in the recumbent position. First, the arterial systolic blood pressure of the thigh was recorded plethysmographically through the use of blood pressure cuffs around the thighs

¹ Janos Olajos, M.D.

² Grete Iversen, M.D.

directly above the knee. Thereafter, the calf blood flow at rest was recorded. Then, reactive hyperaemia was achieved by obstructing arterial inflow to the legs for 3 minutes with the thigh cuffs. The blood pressure cuffs were connected to special pressure tanks which made it possible to fluctuate the pressure quickly from that adequate to occlude veins only to a pressure sufficiently great to occlude both arteries and veins. By thus alternating pressures, several flow peaks were obtained reflective of duration of hyperaemia.

The volume of the plethysmograph was 3,350 ml. The diameter of the piston recorder (F. Palmer, London) was 30 mm. The room temperature was maintained between 23 and 24°C. The temperature of the water in the plethysmograph was 34°C. During recording the arterial inflow to the foot was stopped with a blood pressure cuff placed around the lower leg, immediately distal to the plethysmograph.

The following variables were recorded routinely:

- (1) *arterial systolic blood pressure of the thigh* (measured plethysmographically);
- (2) *rest flow*, i.e. the calf blood flow at rest;
- (3) *blood flow in the calf during reactive hyperaemia*:
 - (a) *first flow*, i.e. the first measured blood flow in the calf after 3 minutes of arterial occlusion, when the pressure of the thigh cuff was momentarily changed from arterio-venous to venous occlusive pressure. *Results presented in this work were mainly based on first flow*;
 - (b) *peak flow*, i.e. the maximum blood flow recorded during reactive hyperaemia;
- (4) the *time interval* in seconds between first flow and maximum flow;
- (5) *pulse amplitudes* in mm during the peak flow;
- (6) *pulse rate* per minute.

All variables, except the arterial systolic blood pressure of the thigh, were recorded twice.

The pulse amplitudes were measured according to the method of Dahn but without optic enlargement of the plethysmogram and without

correction for leg volume. A pulsation of 3 mm corresponded to a volume change of approximately 800 mm³ (Fajgelj *et al.* 1967). The flow values were given in ml./min./100 ml. leg volume.

Immediately following the plethysmographic examination and while the patient was still recumbent, the arterial systolic and diastolic blood pressures in the right arm were recorded. The method described earlier was employed, except for the changes in position. The arm blood pressure was measured only once.

In this study the mean blood pressure has been calculated from diastolic arm blood pressure plus 1/3 of the pulse pressure (Folkow *et al.* 1958).

Plasma cholesterol and triglycerides

Plasma cholesterol concentration was determined according to the method described by Pearson *et al.* (1953) and Boy *et al.* (1969). The cholesterol data were given in mg/100 ml.

Plasma triglycerides were estimated according to the method of Laurell (1966) and Kessler (1967) and were given in millimoles.

A comparison was made between cholesterol and triglyceride determinations from 25 randomly selected plasma samples as done in our own laboratory and in the Clinical Chemical Laboratory of the Sahlgrenska Hospital, Gothenburg, which considers itself to be standardized with the Communicable Disease Centre, Atlanta, Georgia, USA (Cooper 1965). A systemic variance existed regarding results from the two laboratories. Our laboratory averaged about 50 mg/100 ml lower cholesterol, and 0.4 millimoles higher triglyceride values. These differences were statistically significant ($p < 0.001$).

Lipoprotein-electrophoresis

Lipoprotein-electrophoresis was carried out on a randomly selected subsample comprising 10 % of the population. All the blood samples were taken in June after other aspects of the population study had been completed. Samples for electrophoresis were taken under the same

conditions as was the blood for other analyses done in this study. The electrophoretic examination was performed through argarose-gel-electrophoresis (for literature, see Houtsmuller 1969); 1 % argarose and 0.075 M barbital buffer (pH 8.6) were used. After the fractions had separated the gel was immersed for 45 minutes in methanol and water (1:1) to precipitate the fractions before drying and staining (Sudan black).

The interpretation of all lipoprotein-electrophoreses were made by a physician trained in this field.¹

Follow-up examination regarding the peripheral circulation

On the basis of the described measurements of the calf blood flow and in accordance with the criteria stated in chapter 4 of this report, the subjects representative of the upper (n=34) and lower (n=33) 5 % of the total material in regard to quality of peripheral circulation were identified and called for a second examination. This investigation was carried out during spring 1970, immediately after the population study was concluded. At the same time, all who had been diagnosed as intermittent claudication (n=20), according to their responses to the questionnaire previously described, were subjected to a special questionnaire that repeated the earlier questions concerning intermittent claudication. After the second questionnaire had been critically assessed, the data resulting from examination of circulation in the legs were carefully analysed. Existence of any other symptoms and previous diseases was noted. Symptoms involving the loins and the joints aroused special interest.

Thereafter, the following routine examinations were carried out:

Physical status, including inspection of the skin with special regard to any possible trophic changes and varicose veins and perforant insufficiency.

Pulse palpation was done essentially as before. Pulses were palpated in the femoral artery, the

tibial posterior, the dorsal pedis, and the popliteal artery.

Auscultation with stethoscope was done from the umbilicus to the inguen, the inguinal region, the medial side of the thighs, and the popliteal space. Auscultation was also carried out over the subclavian and carotid arteries.

Back status and neurologic status, including examination of the patellar and Achilles tendon reflexes and Lasègue's test, were made routinely on all subjects.

The sitting blood pressure was measured on both right and left arm but otherwise identically with the initial examination.

Lipoprotein-electrophoresis and serum-electrophoresis.

Venous occlusion plethysmography was performed as earlier described and by the same laboratory assistant.

A *walking test* was done according to Lund (1956). The subject was requested to walk on a level linoleum-covered floor in a wide hospital corridor. The walking speed was 100 paces/minute. The patient was dressed in his own clothes, without a jacket, and with shoes on. The distance walked before the appearance of symptoms is referred to as the "symptom-free walking distance". The walk continued for 1000 meters or until stopped by pain. The total walking distance was recorded. Walking tests were supervised by a laboratory assistant who had no information about the patient.

The *exercise test* was carried out principally according to the method described by Wahlund (1948). The test was made while the subject was seated and pedalling a bicycle ergometer (Monark-Crescent AB, Varberg, Sweden). The test began with two minutes pedalling at 300 kpm, followed by two minutes at 600 kpm; thereafter work load was increased to 900 kpm if necessary. The test was designed to increase the heart rate to about 150 beats per minute. As soon as this heart rate was equalled or exceeded, the test was terminated. The test was broken off before the mentioned heart rate if the subject suffered from angina

¹ Anders Grubb, M.D.

pectoris or dyspnoea or if the ECG reaction indicated the need for this. When symptoms of claudication caused premature termination of the exercise test, arm ergometry was substituted. Electrocardiogram, blood pressure, and breathing frequency were recorded during the test at the following times:

- (a) before the exercise
- (b) every second minute during the exercise
- (c) immediately after the exercise
- (d) 5 minutes after the end of the exercise.

All the electrocardiograms were coded according to the Minnesota code by the same researcher who had interpreted the resting electrocardiograms made in connection with the population study.¹

Statistical analyses

Frequency distributions, means, ranges, correlation coefficients, and multiple regression analyses were calculated by computer. The significance of mean differences in quantifiable variables among groups was determined by the application of Student's t-test.

Chi-square was used to examine for the significance of differences among groups in regard to the distribution of values representative of a qualitative variable, except where there were low frequencies, in which condition a binomial test was employed.

In this report statistical significance (p) was tested at the 0.05, 0.01, and 0.001 level.

The levels of significance are identified as:

* = $0.01 < p < 0.05$

** = $0.001 < p < 0.01$

*** = $p < 0.001$.

Unless otherwise stated, statistical comparisons were made between a single group and the total material.

Symbols

n = number

m = mean

SD = standard deviation.

DEFINITIONS

The following terms are defined as used in this study:

Hospitalized myocardial infarction. This term applies to 10 subjects previously hospitalized because of acute myocardial infarction, and they fulfilled the following criteria:

(1) appearance of a pathological Q-wave and/or appearance or disappearance of localized ST-elevations followed by T-wave inversions in one or several of the 12 leads;

(2) two SGOT-values of 55 units or more with the maximum appearing about 24 hours after the beginning of symptoms.

All the subjects had evidenced typical infarction pains according to the criteria formulated by WHO (Rose 1962).

Cerebrovascular disease. This term describes five subjects, three of whom were previously hospitalized. Two of these three were being treated for cerebral haemorrhage with hemiplegia and aphasia; the third had had his condition diagnosed as cerebral thrombosis (Wallenberg's syndrome). Both the other subjects, although not previously hospitalized, had typical medical histories of hemiplegia and dysarthria. One of them continued to evidence some weakness in one arm and was slightly dysarthric, even though about a year had elapsed since his initial illness. The other showed no symptoms and was several months beyond his first episode.

Diabetes mellitus. Eleven members of the study claimed to have diabetes mellitus. In ten of these the diagnoses were verified by hospital records or in doubtful cases with supplementary oral glucose tolerance tests. The eleventh subject was found to have renal glucosuria. Two other individuals evidenced glucosuria; subsequent oral glucose tolerance tests established that both had diabetes mellitus. Thus, twelve subjects were found to be diabetic.

DISCUSSION

In this study the recent recommendations of WHO were used in the epidemiological invest-

¹ Janos Olajos, M.D.

igations of heart and vascular diseases (Rose and Blackburn 1968).

Concerning the cardiovascular questionnaire, it is essential that the original meanings of the questionnaire terms survive translation to another language. Although this requisite is fulfilled, the questions might receive varied interpretations owing to individual differences in level of education, power of concentration, intelligence, and background experience. Angina pectoris has not been identified as an important risk factor for myocardial infarction (Epstein 1965, Simborg 1970). The reason for this paradox is perhaps in part the inability to adequately diagnose angina pectoris by questionnaire. In view of this, we might question the true relation between intermittent claudication, as diagnosed by questionnaire, and the presence of arterial insufficiency of the lower extremities.

The cholesterol and triglyceride data were determined with methods used routinely in our laboratory. Analyses thus done deviated considerably from duplicate sample analyses provided by the reference laboratory. These deviations, however, were systematic. A correction factor was neither introduced nor considered necessary as a consistent method was used in the studied material.

Several of the studied variables are known to vary during a 24-hour period. This has been amply discussed by Tibblin (1967), among others, who pointed out that blood pressure, electrocardiogram, and heart volume can change during the course of the day. Strict adherence to a time-schedule for all examinations from subject to subject eliminated such diurnal variations as sources of error.

However, it was not possible to eliminate seasonal variations as sources of error. The examinations went on for more than a year, except for the warmest period, summer 1969. The lipid data varied with the season in the way described by Carlson and Lindstedt (1968). The cholesterol was lowest during early summer and triglycerides were lowest during autumn.

There were no discernible seasonal variations

in the variables recorded plethysmographically.

Recommendations by WHO concerning measurements of blood pressure were followed (Rose and Blackburn 1968). Despite this, other factors could influence the obtained values rendering it difficult to make valid comparisons with results from other investigations. One such factor is smoking. It is known that blood pressure rises in connection with smoking (Shepherd 1963). Therefore it was considered essential to know, before making cross-study comparisons, whether the subjects had smoked before blood pressure measurement, and if so, how long had elapsed between smoking and measurement. Several authors, Lundman (1966) among them, have found that smokers have lower systolic and diastolic blood pressures than non-smokers. The reason for this, Lundman claimed, was that the subjects had abstained from smoking for some time before the examination. Tibblin (1967) believed that the slightly lower blood pressure in smokers is caused by their smaller amount of body fat than that of non-smokers.

Venous occlusion plethysmography is considered the best method for evaluating the circulation in the extremities in man (Graf and Ström 1959, Greenfield 1960, Hyman and Winsor 1961, Shepherd 1963, Dahn 1965, Fajgelj *et al.* 1967, Bollinger 1969).

The method used by the author was essentially the same as that described by Dahn (1965) and Fajgelj *et al.* (1967). Occlusion of the arterial inflow to the extremity causes reactive hyperaemia when the stasis is released (Bollinger 1969, Shepherd 1963). During reactive hyperaemia, the arterial vascular bed below the cuff is considered to be almost maximally dilated. Three minutes of arterial occlusion has been considered sufficient to produce this dilating effect (Dahn 1965, Bollinger 1969) which has been ascribed to vasoactive metabolic substances. After the period of reactive hyperaemia, the magnitude of the flow is reduced, especially if there is a reduction of the arterial lumen (Shepherd 1963).

Other authors have found that occlusion plethysmography agrees well with angiography in terms of identifying arterial diseases (Dahn 1965, Fajgelj *et al.* 1967). Furthermore, with occlusion plethysmography, it is possible to rather accurately determine whether or not stenoses or occlusions exist in the femoral region.

An important reason why venous occlusion plethysmography was used in the present study is that its reliability is well-documented. Also, availability of the method played a part in its selection. Venous occlusion plethysmography has been the standard method for evaluating extremity circulation for several years at the Malmö General Hospital (Fajgelj *et al.* 1967).

SUMMARY

The methods used in connection with this population study conform to the recommendations of WHO, were routine methods at the supporting institution, or had been tested in connection with the present study. The methods have not been changed during the course of the research. Examinations were performed by experienced technicians. The author took part in, and supervised, the investigation of every subject.

4. RESULTS OF VENOUS OCCLUSION PLETHYSMOGRAPHY

As earlier stated, venous occlusion plethysmography is considered the best method for evaluation of the circulation in the extremities of man. Previous investigations have revealed a relatively good agreement between angiographic findings and findings obtained with venous plethysmography (Dahn 1965, Fajgelj *et al.* 1967).

Number of individuals examined with plethysmography

Venous occlusion plethysmography was carried out satisfactorily in 684 of the 703 subjects who

Table 5. Reasons for exclusion of 19 out of 703 subjects from examination by venous occlusion plethysmography

Amputated (arteriosclerotically caused gangrene)	1
Arthrodesis or contracture of foot or knee joints	3
Refusals	15
Total	19

participated fully in the population study; 19 were not examined (see Table 5).

One of the unexamined 19 had had his left leg amputated shortly before this study began

Table 6. Precision of measurement of different flow variables achieved with venous occlusion plethysmography.

		Systolic blood pressure (thigh)	Amplitude	Rest Flow	First Flow	Peak Flow	Sec. to Peak Flow
Comparison between 2 consecutive examinations. No. of legs=20	Mean	—	—	1.8	21.0	29.4	5.6
	Mean difference	—	—	−0.03	−0.33	0.37	5.62
	SD difference	—	—	0.11	3.59	4.56	2.49
	Coefficient of variation (%)	—	—	4.4	12.1	11.1	31.8
Comparison between 2 examinations performed with 2 months' interval. No. of legs=20	Mean	137	8.1	1.9	23.3	31.3	5.4
	Mean difference	8.50	0.30	±0	−0.94	−0.29	−1.00
	SD difference	11.93	2.47	0.60	3.81	6.55	2.67
	Coefficient of variation (%)	6.2	21.9	22.6	11.7	15.0	35.3

because of thrombosis of the femoral artery with complicating gangrene. A preoperative plethysmography showed arterial obliteration of the right femoral artery also. The other unexamined 18 had normal pulses at palpation, showed no symptoms of intermittent claudication, and their smoking habits and blood lipids did not differ from those of the examined subjects.

Precision of the method

The precision of measurement of different variables achieved with venous occlusion plethysmography was tested in two ways. A

comparison was made between two consecutive examinations at the same impaction of the same subject and also between duplicate examinations with approximately two months intervening. Table 6 records the results (page 19).

The precision, expressed as coefficient of variation, was best regarding first flow and peak flow after 3 minutes of arterial occlusion (Table 6). When testing the results obtained with 2 months intervening, the highest measured flows on each of the two examinations were compared. Consequently, these means differ somewhat from the means of the examinations performed consecutively.

Table 7. Results of venous occlusion plethysmography, various authors, same method.

Author	Total number of legs	Sex	Age	Systolic blood pressure (thigh)
<i>Dahn, I. (1965)</i>				
(Mean $\pm$ SD)				
Clinically healthy arteries	52	Male	45.9 $\pm$ 22.5	143 $\pm$ 27.6
„	52	Female	44.7 $\pm$ 23.9	140 $\pm$ 25.6
Legs with angiographically arterial changes but no obliteration	22		58.1 $\pm$ 8.54	123.0 $\pm$ 30.3
Legs with angiographically obliterated arteries	46		58.2 $\pm$ 9.82	97.6 $\pm$ 23.6
<i>Fajgelj, A. et al. (1967)</i>				
(Mean and Range)				
Legs with angiographically no changes	20	Male and Female	Various	167 (95–240)
Moderate arteriosclerosis	7	„	„	166 (120–220)
Extensive arteriosclerosis	8	„	„	153 (110–215)
Legs with obliteration	35	„	„	161 (80–250)
Present series (Mean $\pm$ SD)	1368	Male	55	142 $\pm$ 23.5

¹ D.m. = Different method.

Comparison between previous examinations with the same method

The plethysmographic method employed in this study was essentially the same as described by Dahn (1965) and Fajgelj *et al.* (1967) who used a venous occlusion plethysmograph with a water-filled system and measured the flows during reactive hyperaemia after 3 minutes of arterial occlusion. The plethysmographic results of their work are compared with those of this study (Table 7).

Dahn found somewhat higher first flows and peak flows during reactive hyperaemia in middle-aged men with clinically healthy vessels

than those reported by the author of this present study. This may be explained by the fact that Dahn's material consisted of subjects with clinically healthy vessels, whereas those investigated in this study had both healthy and diseased vessels. Dahn reports about the same systolic thigh blood pressures as seen in the present study, but noted obviously higher rest flows.

Both Dahn (1965) and Fajgelj *et al.* (1967) made comparisons between angiographic and plethysmographic findings. They found that the flows during reactive hyperaemia, *i.e.* first flows and peak flows, were very much reduced if

Amplitude	Rest Flow	First Flow	Peak Flow	Seconds to Peak Flow
D.m. ¹	3.16±1.54	23.6±8.09	28.8±8.00	—
D.m.	2.87±1.12	19.0±6.64	24.3±8.49	—
D.m.	3.01±1.05	12.7±7.72	16.5±6.87	—
D.m.	3.36±1.37	5.41±2.96	10.8±4.64	—
4.7 (3—9)	2.9 (0.6—4.7)	27.3 (13.7—40.3)	28.9 (17.2—40.6)	4.8 (0—15)
3.8 (2.2—7.0)	3.03 (1.1—5.4)	18.0 (6.6—23.0)	24.4 (21.3—35.8)	10.7 (0—30)
2.3 (1—3.4)	3.98 (2.2—7.0)	15.5 (5.0—25.4)	20.7 (9.7—27.2)	15 (0—30)
1.4 (0—2.6)	3.16 (0.5—7.2)	7.8 (3.5—13.5)	13.5 (5.1—23.1)	24 (0—112)
7.5±2.3	1.9±0.7	20.7±6.4	25.8±8.6	4.4±3.3

there were arteriosclerotic changes in the absence of obliterations. If there was obliteration, the reactive flows were even further reduced. But rest flows were approximately the same in normal persons and in those with diseased vessels.

Plethysmographic criteria of arterial occlusion

In cases where arterial occlusion can be demonstrated angiographically Fajgelj *et al.* (1967) have shown that the following criteria are met:

- (1) amplitude ≤ 3 mm, and simultaneously
- (2) first flow during reactive hyperaemia ≤ 14 ml/minute
- (3) peak flow during reactive hyperaemia ≤ 17 ml/minute.

In the present study, the subjects who fulfilled these three criteria were considered to have an occlusion or a nearly occluding stenosis within the iliofemoral arteries. These subjects have also been examined angiographically, with the exception of one who died immediately after the study and where the diagnosis was verified at autopsy.

Choice of discriminating variable

Investigations performed by other authors have shown that the first flow is the variable best discriminating between individuals with healthy and diseased vessels (Dahn 1965, Fajgelj *et al.* 1967, Bollinger 1969). In the present study, it was considered necessary, because of the number of subjects, to base assignment into groups on a single variable. Initially, an analysis was made of first flow and peak flow in the entire group. However, in view of the earlier research cited above, it was decided to form normal and diseased groups on the basis of first flow alone. Nonetheless, it should be noted that the correlation between first flow and peak flow was good ($r=0.80$).

The dependence of first flow on other variables

Statistical analyses showed that among the investigated variables first flow was significantly related to systolic and diastolic arm blood

Table 8. Correlation coefficient between first flow and other variables. $n=684$.

	First flow
Systolic blood pressure	0.31***
Diastolic blood pressure	0.25***
Mean blood pressure	0.28***
Pulse rate	0.15***
Height	-0.21***
Weight	-0.07

*** = $p < 0.001$.

pressure and to the pulse frequency measured in connection with the plethysmographic recording. Furthermore, there was a significant negative correlation between height and first flow. Table 8 records the correlation coefficients.

The strongest correlation was between first flow and systolic blood pressure. The correlation between first flow and weight was not statistically significant.

The influence of blood pressure, pulse rate, and height on first flow has been assessed statistically with analysis by multiple regression. Although the strongest correlation was between systolic blood pressure and first flow, the mean blood pressure was used to calculate regression coefficients, because this is considered to be the driving pressure. Through these calculations it was possible to construct the following prediction equation:

first flow (dependent) = pulse frequency $\times 0.05$ + mean blood pressure $\times 0.10$ - height $\times 0.18$ + 38.33.

The multiple correlation coefficient was 0.35.

This equation was used to predict the first flow for each individual resulting in standardization of the influence of pulse frequency, mean blood pressure, and height on the observed first flow.

The observed first flow was then compared with the predicted first flow.¹ In all cases, the

¹ Example of estimation of predicted first flow: Individual A with pulse frequency 70/min., mean blood pressure 100 mm Hg, height 180 cm. Predicted first flow equals: $70 \times 0.05 + 100 \times 0.10 - 180 \times 0.18 + 38.33$ (=19.4 ml/min.).

highest first flow in the leg with the poorest circulation was considered observed first flow. Double determinations were made. The observed first flow was divided by the predicted first flow and the resultant quotient was multiplied by 100:

$$\frac{\text{observed first flow}}{\text{predicted first flow}} \times 100.$$

This index was calculated for every subject and, throughout this report, is referred to as the *flow capacity*. There proved to be no significant correlation between flow capacity on one hand and mean blood pressure, height, and pulse frequency, on the other.

Fluctuations in blood pressure during plethysmographic recording

Fluctuations in blood pressure during the recording of the flows could indicate that the mean blood pressure, on which the calculation of the predicted flow was based, was not accurate. For this reason, systolic and diastolic arm blood pressures were determined in 15 randomly selected subjects: (1) during the last 30 seconds of arterial occlusion (determination I); (2) during the first 30 seconds of reactive hyperaemia (determination II); and (3) during the first 30 seconds following the plethysmographic recording (determination III). The last blood pressure measurement (III) coincided with the blood pressure measurement made in the subjects who underwent plethysmography.

The mean difference between II and III was 2.0 ± 3.6 mm Hg. The difference was not statistically significant. A statistical analysis showed that this slight variation in mean blood pressure failed to influence the group division appreciably.

Grouping of the material according to flow capacity

The assignment of the material into groups was based on *flow capacity*. Thus, the influence of blood pressure and pulse frequency was eliminated, regardless of whether that influence was physiologically or patho-physiologically precipitated. In the same way the negative influence of height was eliminated.

The main principle was to assign the population into deciles (Documenta Geigy 1962) of flow capacity and this grouping is presented in Table 9. Table 9 also shows the mean magnitude of the first flow in each decile. In addition to the decile groups, two other groups were formed, *extreme-1* and *extreme-10*. These groups consist of the 5 % of the population with the lowest (*extreme-1*, n=33) and highest (*extreme-10*, n=34) flow capacities and are, in fact, representative of the poorest half of decile 1 and the best half of decile 10.

The results of this study will be expressed in relation to the following subject classifications:

- (1) *decile-groupings* based on flow capacity with the sub-groups *extreme-1* and *extreme-10*;
- (2) *occlusions or stenoses* within the iliofemoral arteries, such diagnoses having been established on the basis of criteria stated in this chapter.

DISCUSSION

Venous occlusion plethysmography provides recordings of several variables. Of the measured flow variables, the circulation at rest showed the weakest relation to the degree of arterio-sclerotic changes (Dahn 1965, Fajgelj *et al.* 1967). The same authors have also proved that there

Table 9. Flow capacity in all deciles with mean and standard deviation of first flow.

Deciles	1	2	3	4	5	6	7	8	9	10
n	67	68	69	69	68	69	69	68	69	68
Flow capacity	≤65	66–76	77–85	86–92	93–98	99–105	106–112	113–122	123–135	≥136
First flow m	11.9	15.6	18.1	18.8	21.0	21.5	23.9	24.6	26.8	31.1
S.D.	4.1	3.5	4.3	4.3	3.9	4.4	4.8	3.9	4.4	5.5

is a good correlation between flows measured during reactive hyperaemia (first flow and peak flow) and the degree of arteriosclerosis.

The magnitude of the flows during reactive hyperaemia can be considered a good measure of the reserve capacity of the arterial tree (Dahn 1965, Bollinger 1969).

From the epidemiological point of view, it does not matter whether the first flow or the peak flow is used as the discriminating variable. Since previous investigations (Dahn 1965) found the first flow to be more strongly related to the degree of arteriosclerosis, the first flow was selected. However, the correlation between the first flow and the peak flow was quite strong.

As a reflection of the morphology of the arterial tree, the first flow should form an adequate basis for a class assignment of the population, provided that the first flow is dependent upon arterial tree morphology only. Our own investigations, however, showed that the first flow was significantly related to the arm blood pressure, pulse frequency, and height.

The relation of systemic blood pressure to the reactive flows has been studied earlier by, among others Wilkins and Eichna (1941) who found that the flows varied with the amplitude of the blood pressure.

The influence of the pulse rate on the magnitude of the first flow is probably secondary to a larger cardiac output per minute in those with high pulse frequency, thereby increasing peripheral flow.

The explanation of the negative correlation between height and first flow is not clear. Tall individuals in the upright position have a higher pressure in the lower extremities than do short ones. This might possibly cause an adaptive hypertrophy of the arterial wall (Folkow, personal communications).

The calculation of *flow capacity* implied standardization for the influence of systemic blood pressure, pulse frequency, and height on the first flow. Possible patho-physiological connections between these variables and the

magnitude of the first flow were thus eliminated.

The material was divided into deciles of flow capacity based on the first flow during reactive hyperaemia. It was observed that when classifying according to first flow, there is a tendency for subjects with angiographically healthy vessels to overlap those with diseased vessels (Dahn 1965, Fajgelj *et al.* 1967). Such an overlapping was judged to be of no importance from the epidemiological point of view, since those with the most advanced arteriosclerosis could be expected to belong to the group with the lowest flow capacity.

Judging from autopsy studies, it seems certain that arteriosclerosis is the predominant cause of symptoms of arterial disease in 55-year-old men (Sternby 1968). It appears logical that reduced flow capacity should be evident in arteriosclerotic disease, and that the reduction could be conditioned by morphological changes in the arteries and arterioles above the plethysmograph cuff (arteriosclerotic plaques, thromboses, wall hypertrophy, fibrosis, sclerosis).

SUMMARY

Of the variables measured at venous occlusion plethysmography, other authors have proved that the first flow during reactive hyperaemia is the variable best discriminating between subjects with healthy and those with diseased arteries. However, the first flow appeared to be significantly related to the systemic blood pressure, pulse frequency, and height. The influence of these variables on the first flow was mathematically accounted for, and for every subject, an index called *flow capacity* was calculated. The *flow capacity* (the ratio between observed and predicted first flow) is considered an adequate measure of the reserve function of the arterial tree, thereby indirectly reflecting the possible existence of arterial disease. In this study, it was accepted as a principle that among 55-year-old Swedish men the predominant cause of arterial disease is arteriosclerosis.

5. VALIDATION OF THE WHO QUESTIONNAIRE AND REPORTS OF CLINICAL AND ELECTROCARDIOGRAPHIC FINDINGS RELATED TO VENOUS OCCLUSION PLETHYSMOGRAPHY

In the book *Cardiovascular Survey Methods* Rose and Blackburn (1968) established that available techniques for studying the peripheral vascular diseases are quite limited and that conventional clinical methods for evaluating peripheral pulses and peripheral circulation are not sufficiently reliable.

In this chapter an effort is made to:

(1) evaluate the accuracy of the cardiovascular questionnaire in diagnosing intermittent claudication (Rose and Blackburn 1968);

(2) analyse plethysmographically diagnosed occlusion and near-occluding stenosis in the iliofemoral arteries;

(3) evaluate the clinical importance of reduced flow capacity;

(4) examine laboratory and clinical findings in cases of myocardial infarction, cerebrovascular disease, diabetes mellitus, and occlusions in the iliofemoral arteries;

(5) relate electrocardiographic findings to plethysmographic results.

RESULTS

Intermittent claudication diagnosed by questionnaire

Based on the responses obtained with the aid of the cardiovascular questionnaire, 20 subjects (2.8 %) were diagnosed as having intermittent claudication. These were requested to return for further investigations. Table 10 provides a

description of this group and analysis of reasons for mentioned symptoms of claudication in connection with the population study. In Table 10 the subjects have then been ranked from 1 to 20 according to increasing magnitude of flow capacity.

A careful analysis of medical histories showed 8 of these 20 subjects to have typical symptoms of claudication. In 6 of the 8, symptoms were considered to be due to arterial insufficiency. In two cases, arterial insufficiency could not be demonstrated. In one of the two cases (ID 208) Parkinson's disease and low back pain were diagnosed and the other (ID 388) had angiospastic symptoms with gouty arthritis as possible explanations for leg pains.

In two cases in the claudication group, arterial insufficiency could not be excluded. One (ID 99) had a flow capacity of only 55 but showed no signs of occlusion, clinically or plethysmographically, and his walking test was negative. The remaining case (ID 465) probably had a haemodynamically important aortic stenosis. His response to the walking test was pathological, but the flow capacity was relatively high.

One individual (ID 174) did not meet the plethysmographic criteria for occlusion, but had moderate symptoms of claudication, a pathologic walking test, and a flow capacity of 68. In this case, there were clinical signs of occlusion with no pulses from the femoral artery downwards. His moderate symptoms, in spite of severe clinical signs, might be explained by the possible

Table 10. Intermittent claudication according to WHO questionnaire. Analysis of reasons for mentioned complaints.

Identification No.	Flow capacity (poorest leg)	Re-examination					
		Typical inter-mittent claudi-cation		Pulse palpation			
				Femor	Popl.	Tib. post.	Dors. ped.
329	Missing data (Md)	+	R	+	—	—	—
			L	—	Amputated		
26	13	+	R	+	—	—	—
			L	+	—	—	—
688	14	+	R	+	—	—	—
			L	+	—	—	—
471	19	+	R	+	+	+	+
			L	+	+	+	+
119	50	+	R	+	+	+	+
			L	—	—	—	—
99	55	—	R	+	+	+	+
			L	+	+	+	+
174	68	+	R	—	—	—	—
			L	+	+	+	+
31	69	—	R	+	+	+	—
			L	+	+	+	—
465	73	?	R	+	+	+	+
			L	+	+	+	+
208	81	+	R	+	+	+	+
			L	+	+	+	+
327	83	—	R	+	+	+	—
			L	+	+	+	—
133	88	—	R	+	+	+	+
			L	+	+	+	+
110	89	—	R	+	+	+	+
			L	+	+	+	+
515	93	—	R	+	+	+	+
			L	+	+	+	+
436	95	—	R	+	+	+	+
			L	+	+	+	+
216	102	?	R	+	+	+	+
			L	+	+	+	+
199	108	—	R	+	+	+	+
			L	+	+	—	—
388	123	+	R	+	+	—	+
			L	+	+	—	+
325	125	—	R	+	+	+	+
			L	+	+	+	+
370	144	—	R	+	+	+	+
			L	+	+	+	+

¹ A comparison was made between first flow at repeated plethysmography and the first flow on which flow capacity

(peripheral circulation)

Murmurs (iliofemoral arteries)	First flow at repeated plethysmography ¹	Symptom-free walking distance	Explanation for complaints of intermittent claudication
—	(Md)	(Md)	Arterial insufficiency
—	St. quo	160	Arterial insufficiency
—	St. quo	240	Arterial insufficiency
+	St. quo	400	Arterial insufficiency
+	St. quo	200	Arterial insufficiency
—	St. quo	1000	Calf pain at rest and when walking. Pes planus. Varicose veins. Arterial insufficiency?
—	St. quo	950	Arterial insufficiency
—	+	1000	Pains in lower legs at rest and when walking. Aethiology uncertain.
—	St. quo	760	Aortic stenosis. Arterial insufficiency?
—	+	560	Parkinson's disease. Low back pain.
—	+	1000	(Did not understand the questions.) Low back pain.
—	St. quo	1000	Low back pain.
—	St. quo	1000	(Did not understand the questions.)
—	St. quo	1000	Psychic symptoms. Neuralgic foot pain.
—	St. quo	1000	Psychic symptoms. Disturbed concentration.
—	St. quo	1000	Mental debility.
—	—	1000	Cramp of left lower leg. Disturbed sleep. Occlusion of arteries of left lower leg?
—	St. quo	1000	Angiospastic symptoms in hands and feet. Gouty arthritis.
—	+	1000	(Did not understand the questions.)
—	—	1000	Coxalgia (arthrosis deformans).

was based. Difference ≥ 2 ml/min is recorded with + or —.

existence of an especially good system of collateral vessels.

Low back pain, mental problems, and misinterpretation of the questions were otherwise the most common explanations of the false claudication symptoms.

Plethysmographically diagnosed occlusions in the iliofemoral arteries

Based on the plethysmographic criteria of occlusion accepted in this study, the diagnosis of iliofemoral occlusion was established in 8 subjects (1.1 %). The diagnosis was verified angiographically in 7, and at autopsy in one. A focused follow-up study of this group yielded the results reported in Table 11.

Here we find 5 of the 6 questionnaire-diagnosed subjects, who were found to have intermittent claudication caused by arterial insufficiency. Furthermore, Table 11 describes 3 subjects who claimed to have not had any symptoms of claudication. Their absence of subjective symptoms is due in all cases to the existence of concurrent diseases which limit their ability to move. Two subjects had angina pectoris and residual symptoms after myocardial infarction and cerebrovascular disease. The third subject had had an operation for laryngeal cancer and had also a ventilatory insufficiency. The occlusion group consisted of those with severe illnesses and their functional impairment, as a rule, was not due solely to their peripheral

Table 11. Clinical status of subjects with occlusion or near occluding stenosis in the iliofemoral arteries. $n=8$.

Identification No.	Major diagnosis	Additional diagnosis	Intermittent claudication (questionnaire)	Pathologic walking test	Flow capacity
26	Occlusion bilat.	Status post infarctum cordis	+	+	13
119	Occlusion left	Status post infarctum cordis	+	+	50
329 ¹	Occlusion bilat.	Stenosis in arterie carotis amb.	+	Missing data (Md)	(Md)
344	Occlusion right	Status post infarctum cordis+Haemorrhagia cerebri sequelae	—	+	50
366	Stenoses bilat.	Cancer laryngis (operata)	—	+	49
471	Stenoses bilat.	Morbus cordis arterioscleroticus	+	+	19
634	Stenosis right	Status post infarctum cordis+Thrombosis cerebri sequelae	—	+	47
688	Occlusion bilat.	Diabetes mellitus	+	+	14

¹ Plethysmographic examination a few months before the population study. Angiography revealed bilateral occlusion.

² Exercise test: Minn. code 11-3 and angina pectoris.

vascular disease. Four of the 8 had previously had myocardial infarctions. Two others had either at rest or in exercise ECG-abnormalities indicative of coronary artery disease.

The blood pressure was determined at the follow-up investigation on both the right and left arm. No differences above 10/5 mm Hg were found.

Clinical importance of reduced flow capacity

In Table 12 the material has been divided into deciles of flow capacity. The frequencies are also stated for all the subjects. Myocardial infarction and cerebrovascular disease were more common in decile 1 than in the total material. Half of the subjects with diabetes mellitus

were assigned to either of the two lowest deciles. There was no parallel between absence of one of the foot pulses or symmetric absence of one foot pulse and the magnitude of the flow capacity.

Both subjects with myocardial infarction, cerebrovascular disease, and diabetes mellitus were also in the deciles with high flow capacity, which means that unusually good peripheral circulation can prevail in some subjects with these diseases.

Table 13 shows further comparisons between certain findings in the medical histories and the magnitude of the flow capacity. Here, the material has been divided in a way different from Table 12. Comparisons with the occlusion group

	Pulse palpation				Murmurs (ilio-femoral arteries)	ECG at rest Minn. code	Blood pressure right arm
	Fem.	Popl.	Tib. post.	Dors. ped.			
R	+	—	—	—	—	1—1—4	110/80
L	+	—	—	—	—	5—2	
						6—3	
R	+	+	+	+	—	1—1—4	130/75
L	—	—	—	—	—	4—2	
						5—3	
						8—3	
R	+	—	—	—	—	0	185/95
L	+	Amputated					
R	+	—	—	—	—	4—3	225/140
L	+	+	—	—	—	5—3	
R	+	+	+	+	+	2—3	175/80
L	+	+	+	+	+		
R	+	+	+	+	+	1—3—3	170/105
L	+	+	+	+	+	3—1	
						4—4	
						5—3	
						8—3	
R	+	+	+	—	+	1—2—4	145/75
L	+	+	+	—	—	4—3	
						5—2	
R	+	—	—	—	—	0 ²	180/75
L	+	—	—	—	—		

Table 12. Medical history and pulse palpation in various deciles of flow capacity

No palpable pulses																			
Decile	n	Myo- cardial infarction		Cerebro- vascular disease		Diabetes mellitus		Femor.		Tib. unilat.	Tib. bilat.	Dors. p. unilat.	Dors. p. bilat.	Tib. post. + dors. ped. same foot					
		n	%	n	%	n	%	n	%	n	%	n	%	n	%				
1	67	4*		3*		3		1		3		3		8		13		4**	
2	68	0		0		3		1		6		3		12		4		1	
3	69	1		0		1		0		3		1		8		10		0	
4	69	1		0		0		0		3		3		4		8		0	
5	68	1		0		2		0		2		3		11		6		0	
6	69	0		0		0		0		2		1		6		8		0	
7	69	1		1		1		0		3		1		5		8		0	
8	68	0		0		1		0		2		1		4		10		0	
9	69	1		0		1		0		1		3		4		9		1	
10	68	0		1		0		0		2		3		6		6		0	
Missing data ¹	19	1		0		0		1		1		2		3		2		1	
Total population	703	10 (1.4)		5 (0.7)		12 (1.7)		3 (0.4)		28 (4.0)		24 (3.4)		71 (10.1)		84 (12.0)		7 (1.0)	

¹ Not examined plethysmographically.

*=0.01 < p < 0.05, **=0.001 < p < 0.01 compared with the total material.

have also been made. Seven of the 8 subjects in the group with diagnosed occlusion also belonged to the extreme-1 group. This means that if those with occlusions were excluded, the low flow capacity group would not differ from the material as a whole. In the extreme group with the best flow capacity (extreme-10), there

was no subject with any of the diagnoses mentioned in Table 13.

In order to form an opinion of the functional importance of extremely low flow capacity, a standardized walking test was given to all members of the groups extreme-1 and extreme-10. Table 14 reports the results. It includes data

Table 13. Medical history accompanying occlusion and at different magnitudes of flow capacity.

Diagnoses	Grouping based on flow capacity							Not examined plethysmo- graphically n=19	Total material n=703	
	Occlusion n=8		Extreme-1 n=33		Middle group n=617		Extreme-10 n=34			
	n	%	n	%	n	%	n		n	%
Myocardial infarction	4***	(50.0)	4**	(12.1)	5	(0.8)	0	1	10	(1.4)
Cerebrovascular disease	2**	(25.0)	2*	(6.0)	3	(0.5)	0	0	5	(0.7)
Diabetes mellitus	1	(12.5)	2	(6.0)	10	(1.6)	0	0	12	(1.7)
Intermittent claudication (questionnaire)	5***	(62.5)	6***	(18.2)	13	(2.1)	0	1	20	(2.8)
Angina pectoris (questionnaire)	4***	(50.0)	6*	(18.2)	35	(5.7)	0	1	42	(6.0)

*=0.01 < p < 0.05, **=0.001 < p < 0.01, ***=p < 0.001 compared with the total material.

Table 14. Results of walking test, extreme-1, and extreme-10.

	Terminated because of typical intermittent claudication	Terminated because of angina pectoris + inter- mittent claudication	Terminated because of angina pectoris alone	Totally	
	n	n	n	n	%
Extreme-1 n=33	4	3	2	9	(27.3)
Extreme-10 n=34	0	0	1	1	(2.9)

from the 7 subjects in the extreme-1 group who had earlier been given the diagnosis of occlusion. The walking test failed to provoke symptoms of claudication in subjects with extremely low flow capacity but without occlusion. Two subjects in extreme-1 had to terminate the walking test because of angina pectoris and one subject in group extreme-10 had to terminate the walking test for the same reason. This was later confirmed by exercise-ECG.

Laboratory and clinical findings in myocardial infarction, cerebrovascular disease, diabetes mellitus, and occlusion in the iliofemoral arteries

Table 15 shows that the flow capacity was lowest in cases of documented occlusion, but that it was also significantly reduced in subjects

with histories of myocardial infarction and diabetes mellitus.

Systolic and diastolic *blood pressures* were not significantly increased with myocardial infarction, but were with cerebrovascular disease. Systolic blood pressure was significantly elevated in cases of occlusion, but diastolic blood pressure was not.

The relative *heart volume* was significantly increased in those with histories of myocardial infarction and in cerebrovascular disease.

Cholesterol and *triglyceride* concentrations were significantly increased in those with myocardial infarctions or cerebrovascular disease. Subjects with iliofemoral occlusion had a moderate increase of cholesterol and a significant increase of triglycerides. Among those with

Table 15. Flow capacity, blood pressure, heart volume, and blood lipids in different diseases in the subjects.

Diagnosis	n		Flow capacity	Blood pressure		Heart volume		Cholesterol	Triglycerides
				Systolic	Diastolic	Total	Relative		
Myocardial infarction	10	m	73.4 ^{1**}	150.5	87.5	1006 ^{1*}	532 ^{1**}	287.5 ^{1**}	2.88 ^{1***}
		SD	36.3	36.9	22.9	278	134	65.5	3.22
Cerebrovascular disease	5	m	82.2	196.0 ^{***}	121.0 ^{***}	1150.0 ^{1***}	600.0 ^{1***}	286.0 ^{**}	2.00 ^{**}
		SD	41.1	24.9	13.9	176.3	115.5	40.5	2.25
Diabetes mellitus	12	m	80.3 ^{**}	146.7	81.3	916.7	476.7	229.6	1.30
		SD	30.4	20.9	10.7	209.3	92.5	42.2	0.78
Occlusion	8	m	34.6 ^{1***}	165.0 ^{***}	90.6	965 ¹	507 ¹	276.4 ^{1*}	2.41 ^{1***}
		SD	18.1	35.9	22.8	248	118	63.4	2.20
Total material	703	m	100.0 ²	138.7	83.8	885 ³	464 ³	246.6 ³	1.08 ³
		SD	28.1	22.5	14.5	174	78	43.9	0.73

¹ Missing data for one subject. ² Missing data for 19 subjects. ³ Missing data for two subjects.

* = 0.01 < p < 0.05, ** = 0.001 < p < 0.01, *** = p < 0.001 compared with the total material.

Table 16. ECG-findings at rest accompanying various disease entities found in the subjects.

Diagnosis	n	Minnesota-code					
		I: 1–3 (QRS)		IV: 1–3 (ST)		V: 1–3 (T)	
		n	%	n	%	n	%
Myocardial infarction	10	6***	(60)	4**	(40)	6***	(60)
Cerebrovascular disease	5	1	(20)	4***	(80)	4***	(80)
Diabetes mellitus	12	1	(8)	1	(8)	0	
Occlusion	8	4***	(50)	3*	(38)	5***	(62.5)
Total material	703	11	(1.6)	43	(6.1)	39	(5.5)

*=0.01 < p < 0.05, **=0.001 < p < 0.01, ***=p < 0.001 compared with the total material.

diabetes mellitus, cholesterol and triglyceride concentrations did not significantly differ from those of the total material.

ECG-findings are presented in Table 16. Pathological QRS-patterns, ST-, and T-changes were approximately equally prevalent among iliofemoral occlusion subjects and myocardial infarction subjects. Deviations in ST- and T-wave segments were predominantly found in company with cerebrovascular disease. The diabetes mellitus group did not differ electrocardiographically from the total material.

Coincidence of the diagnoses reported in Tables 15 and 16 existed in several cases; this is presented in Figure 1.

Electrocardiographic findings related to plethysmographic results

Table 17 presents comparison between electrocardiographic findings at rest and the magnitude

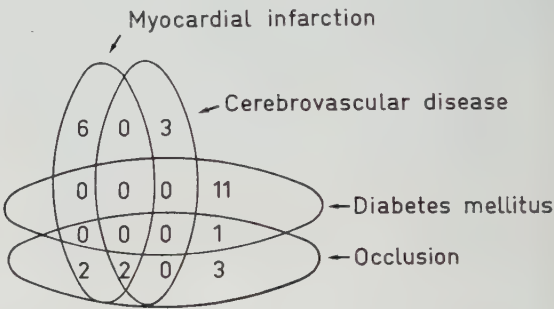


Fig. 1. Co-existence of diseases in the population. n=28.

of the flow capacity. A comparison of these variables was also made with the iliofemoral occlusion groups. The Minnesota-code is quoted regarding QRS-abnormalities, ST-changes, and T-changes.

All the reported ECG-changes were significantly more common in iliofemoral occlusion than in the total material. In the extreme-I group,

Table 17. ECG at rest according to Minnesota-code accompanying occlusion, at different magnitudes of flow capacity, and in the total material.

Minnesota-code	Occlusion		Grouping based on flow capacity						Not examined plethysmographi- cally n=19	Total material		
			Extreme-1 n=33		Middle group n=617		Extreme-10 n=34			n=703		
	n	%	n	%	n	%	n	%		n	%	
I: 1–3 (QRS)	4***	(50)	4***	(12.1)	7	(1.1)	0		0		11	(1.6)
IV: 1–3 (ST)	3*	(38)	9***	(27.3)	34	(5.5)	0		0		43	(6.1)
V: 1–3 (T)	5***	(62.5)	9***	(27.3)	29	(4.7)	0		1		39	(5.5)

*=0.01 < p < 0.05, **=0.001 < p < 0.01, ***=p < 0.001 compared with the total material.

the number of pathological QRS-findings was as great as among those with iliofemoral occlusion. The ST- and T-changes were significantly more common in the extreme-1 group than in the total material. In the extreme-10 group all the ECG-codes at rest were normal.

The *exercise test* was made in both of the extreme groups. Four subjects in the extreme-1 group with normal ECG at rest had ST-changes of type 11-3 upon exercise. In two of these, there were also T-changes, type 12-3. Two of the four subjects in extreme-1 reacted with typical angina pectoris at the exercise test. All four had normal blood pressure at rest.

In the extreme-10 group there were ST- and T-changes in three subjects. In one subject, there were ST-changes, type 11-2; in two subjects, type 11-3 changes in the ST-segment were noted. In these subjects, T-changes, type 12-2 and 12-3, also appeared. Two of the individuals with ST-changes in extreme-10 had elevated blood pressure at rest and one reacted with typical angina pectoris.

DISCUSSION

Questionnaires of the type recommended by WHO (Rose and Blackburn 1968) have been widely used in epidemiologic investigations of cardiovascular diseases. The reliability of such instruments for diagnosing ischaemic heart disease must be questioned, as angina pectoris is not considered to be one of the important risk factors for myocardial infarction. Analogous with this, it seems likely that there will be some incorrect diagnoses of arterial obliterations of the lower extremities when the diagnosis is based on questionnaire alone, as has been done in previous investigations (Fodor *et al.* 1968).

In this study, the diagnosis of intermittent claudication was based on the applied questionnaire which was a translation of that recommended by Rose and Blackburn (1968). Twenty subjects received this diagnosis. With a focused follow-up study comprising a much more

thorough and distinct medical history, it was possible to find symptoms of typical intermittent claudication in only 8 of the 20; in 6 of these 8, the cause of the symptoms was judged to be arterial insufficiency (occlusion of or almost occluding stenosis of the iliofemoral arteries). In the two remaining cases, there were other reasonable potential explanations for symptoms of claudication. In one, a previously unidentified Parkinson's disease was discovered; this subject also had a history of chronic low back pain. The last subject had a medical history of angiospastic symptoms localized to hands and feet, and also gouty arthritis. It is not clear why the conditions diagnosed in these latter two subjects precipitated symptoms of claudication. However, Spanos and Andrew (1966) reported symptoms indicative of claudication in patients with lower back pain ailments (ruptured disc).

Muscular pains, particularly in those with psychic symptoms, low back pain, and joint ailments were common findings among subjects examined with the focused study and who had no typical symptoms of intermittent claudication.

There is no doubt that some subjects had misunderstood the questionnaire items. One of these could not recall why he had complained of symptoms in the lower extremities.

Anaemia (Pickering and Wayne 1934) or collagenosis (Golding 1970) as causes of claudication symptoms could not be demonstrated in any case. Haemoglobin values and serum electrophoretic tests were within normal limits.

The prevalence of occlusion in the iliofemoral arteries is difficult to establish with certainty in clinical materials. Arteriography seems to be the most suitable method for an exact evaluation, but is not suitable as a screening method because of the risk of complications (Lang 1963, McGraw 1963, Kottke *et al.* 1964). With the previously mentioned plethysmographic criteria of occlusion or near-occluding stenosis (see chapter 4) 8 of the 20 subjects were diagnosed as peripheral artery insufficiency. The diagnosis was verified in 7 of the 8 with angiography and

in the eighth at autopsy. The prevalence of occlusions or near-occluding stenosis within the iliofemoral arteries was 1.1 %, which is probably somewhat lower than that reported by Widmer and Glaus (1970), who found an occurrence rate of 1 % in men aged 40–50 and an age-related increase to 7 % in men 65–74 years of age.

In the occlusion group, only 5 of the 8 subjects had medical histories of intermittent claudication. The other 3 had palpable foot pulses but auscultatory stenoses. A battery of medical history, auscultation, and pulse palpation therefore could detect the disease in all of these 8 subjects.

In one, the medical history showed typical claudication, and there were palpable signs of occlusion. However, the plethysmographic criteria of occlusion were not met. Technically unsatisfactory recording or unusually good collateral circulation seemed logical explanations for the obtained plethysmographic results. At a plethysmographic examination in connection with the follow-up investigation of the peripheral circulation this subject fulfilled the criteria of occlusion.

In the 5 % of the material with the poorest flow capacity, it was not possible to demonstrate more than 8 cases of occlusion with the aid of medical history, pulse palpation, auscultation, and plethysmography.

Therefore, *the prevalence of occlusions in the iliofemoral arteries should, in 55-year-old men, be very close to 1.1 %.*

Neither pulse palpation of the foot nor the questionnaire gave an adequate conception of the arterial reserve function. The walking test proved to be valid in cases where there was occlusion, but did not provide accurate information regarding arterial reserve function in cases of extremely low flow capacity in the absence of occlusion. Consequently, it seems that overt symptoms of arterial insufficiency are delayed until advanced stenosis or total obliteration have evolved. However, the walking test may in some

instances be normal even if there are occlusions angiographically (Fajgelj *et al.* 1967).

Autopsy studies and clinical investigations have been made in order to elucidate the associations among arteriosclerosis in various vascular regions. Some authors have been able to prove through autopsy studies that arteriosclerosis may vary considerably from one vascular region to another (Duguid and Robertson 1955, Baker *et al.* 1961). Other such studies have demonstrated the simultaneous existence of stenosis of coronary vessels and of the carotid, vertebral, and iliac vessels. This latter finding supports the concept that arteriosclerosis is a systemic disease (Mitchell and Schwartz 1962). Sternby (1968) found a rather strong relation between presence of arteriosclerotic changes in the iliofemoral arteries and in the coronary arteries. The relation was not as strong between the presence of disease in the iliofemoral arteries and in the cerebral arteries.

Clinical investigations also have been carried out to clarify the connection between arteriosclerosis of the lower extremities and of other vascular regions (McDonald 1953, Selvaag 1956, Lozada *et al.* 1959, Juergens *et al.* 1960, Singer and Rob 1960, Boyd 1962, Tillgren 1965, Blümchen *et al.* 1966, Schütz 1967, Erdweg and Maurer 1969, Reimer *et al.* 1969, Grunewald *et al.* 1970). With the aid of various methods, including medical history, clinical measurements, and electrocardiographic techniques, it was found that those with arterial occlusions of the lower extremities had an elevated incidence of coronary artery disease and of myocardial infarction and also a lower survival rate after myocardial infarction. Furthermore, people with diseases of the peripheral vessels had morbidity and mortality rate due to myocardial infarction that were in excess of such rates due to cerebrovascular disease (Singer and Rob 1960).

Several authors, such as Sternby (for literature, see Sternby 1968), have found strong links between hypertension and arteriosclerosis and between diabetes mellitus and arteriosclerosis.

Hypertension and diabetes, either singly or together, may accompany a distinctly increased degree of arteriosclerosis. These diseases certainly cannot be identified as the causes of arteriosclerosis, because advanced arteriosclerosis can exist in the absence of both. None the less, there is little doubt that hypertension and diabetes mellitus hasten the natural course of arteriosclerosis (Robertson and Strong 1968).

In this study, it was noted that half of the subjects with occlusions in the iliofemoral arteries had suffered at least one myocardial infarction. Furthermore, there was a significantly higher prevalence of ECG-abnormalities indicative of coronary artery disease in subjects with extremely low flow capacity than there was in the total material. The present study supports the theory that both clinically manifested and sub-clinical arterial insufficiency of the extremities and of the coronary arteries often co-exist. These findings argue in favour of a general spread of the arteriosclerosis.

On the other hand, we noticed that some of the subjects who had had myocardial infarction demonstrated a flow capacity equal to or even higher than that in the total material. A localized arteriosclerosis thus also appears to exist.

Some of the risk factors for cardiovascular disease have been mentioned in this chapter and are thoroughly discussed in the next chapter. At this point, it should be stressed that the relatively uniform risk factor patterns that accompany diagnoses of myocardial infarction, cerebrovascular disease, and occlusions in the iliofemoral arteries could be partly explained by the observed co-existence of two or more of these diseases. Cholesterol and triglyceride values showed essentially the same pattern in the three diseases, whereas hypertension was

more specifically concomitant with cerebrovascular disease (Bjurulf 1964). The three diseases consequently showed a relatively homogenous lipid pattern but with differences in blood pressure. It is also of interest to note that the diabetes mellitus group differed hardly at all from the total material in regard to all measured variables, except for a reduced flow capacity.

SUMMARY

Of 703 55-year-old men, 20 (2.8 %) were diagnosed as intermittent claudication with the WHO questionnaire. Arterial flow insufficiency could be demonstrated in only 6 of these subjects. Three other subjects who claimed no symptoms of claudication on the questionnaire were later found to have arterial insufficiency. Either occlusion or near-occluding stenosis in the iliofemoral arteries was judged to exist in 8 subjects (1.1 %). The diagnoses were made by medical history, pulse palpation, and venous occlusion plethysmography with verification in 7 cases by angiography, and in one case at autopsy.

Co-existence of myocardial infarction, and/or cerebrovascular disease, and/or peripheral arterial occlusion was noticed in several cases. Signs of general spread of arteriosclerosis were quite common, even though a few subjects showed more limited arteriosclerosis.

The cholesterol and triglyceride values showed a relatively homogenous pattern in subjects with myocardial infarction, cerebrovascular disease, and peripheral arterial occlusion. The highest blood pressure was noted in cerebrovascular disease.

The diabetes mellitus group did not differ appreciably in any measured parameter from the average of the total material, except for a reduced flow capacity.

6. RELATION OF VENOUS OCCLUSION PLETHYSMOGRAPHY TO RISK FACTORS

From the methodological aspect it is easier to evaluate the circulation in the legs than that in either the myocardium or the brain. Despite this, the relation between the so-called risk factors and peripheral vascular disease has been studied to a lesser extent than has the relation between risk factors and coronary artery disease. This is probably because it is difficult to obtain objective data that will verify poor circulation as a reflection of peripheral arteriosclerosis.

Several studies have been published showing that some of the factors which relate well to coronary artery disease are also risk factors for the development of arterial occlusion in the arteries of the legs (Azen *et al.* 1956, Nestel 1960, Keen *et al.* 1965, Westlund and Nicolaysen 1966, Widmer *et al.* 1969, Wollenweber *et al.* 1971). Such studies also indicate a positive relation between peripheral arterial occlusions and diabetes mellitus, hypercholesterolaemia, hypertriglyceridaemia, high concentration of beta-lipoproteins, hypertension, and heavy consumption of cigarettes. But most authors have studied only one or a few risk factors simultaneously.

In this chapter, the following factors will be analysed: plasma cholesterol and triglycerides, lipoprotein abnormalities, smoking, habitual physical inactivity, weight and stress. Hypertension is superficially treated because the influence of blood pressure on the flows during reactive hyperaemia has been eliminated from the calculation of flow capacity. In instances

where flow capacity deciles 2–9 did not significantly differ from the total material in a given variable, the deciles were considered as a single group.

For purposes of analysis, the material was grouped on the basis of flow capacity. Comparisons were also made with the small sub-group, whose members had occlusion in the iliofemoral arteries.

RESULTS

Cholesterol and triglycerides

Plasma cholesterol and triglyceride concentrations in cases of occlusion in the iliofemoral arteries and in different magnitudes of flow capacity are presented in Table 18. The mean cholesterol values were moderately increased in the occlusion group but no relation could be demonstrated between the magnitude of the flow capacity and the level of cholesterol. The mean triglyceride concentration was significantly increased in the occlusion group, and a moderate mean increase was evident in the extreme-1 group. The higher triglyceride value in the first decile was due mainly to the fact that all 8 occlusion cases were in the first decile and made an inordinate contribution to the mean increase. There was a slight trend towards successively decreasing triglyceride values with increasing flow capacity. The lowest mean triglyceride concentration was found in the extreme-10 group, but it was not significantly lower than in the total material.

Table 18. Cholesterol and triglycerides at occlusion and at different magnitudes of flow capacity.

		Occlusion	Extreme-1	Decile 1	Deciles 2-9	Decile 10	Extreme-10	Total material
	n	8 ¹	33 ¹	67 ¹	549	68	34	703 ²
Cholesterol (mg/100 ml)	m	276*	247	250	247	247	252	247
	SD	105	52	49	42	42	48	44
Triglycerides (millimoles)	m	2.41***	1.37*	1.21	1.07	0.97	0.92	1.08
	SD	2.19	1.18	0.91	0.71	0.44	0.36	0.73

¹ Missing data for 1 subject. ² Missing data for 2 subjects.

* = 0.01 < p < 0.05, *** = p < 0.001 compared with the total material.

Lipoprotein abnormalities

Lipoprotein electrophoresis was carried out in the extreme-1 group and in the extreme-10 group and also in a representative sample from the material consisting of 70 randomly selected subjects. Lipoprotein electrophoresis was carried out in 7 of the 8 occlusion cases.

The hyper-lipoproteinaemias were classified according to Fredrickson's system (Fredrickson *et al.* 1967), and the results are shown in Table 19. The frequency of unclassified elevated pre-beta lipoproteinaemia is also recorded in Table 19. The prevalence of lipoprotein abnormalities was significantly higher among those with occlusion. One case of elevated pre-beta fraction was found in those without occlusion but with extremely low flow capacities. Lipoprotein abnormalities in those with extremely low flow capacity, but no occlusion, were not more

prevalent than in those with extremely high flow capacity, the prevalence being essentially the same as in the total material.

Smoking

The relation between smoking and magnitude of flow capacity is shown in Figure 2 (page 38). The material was assigned into deciles of flow capacity and the prevalence of various smoking habits stated for every decile. There were fewer subjects who had never smoked in the deciles with lower flow capacities than in the deciles with higher flow capacities, but there were no significant differences between the different deciles and the total material.

The prevalence of ex-smokers was significantly lower in decile 1 than in all other deciles compared with the total material (p < 0.01).

The number of smokers in decile 1 was

Table 19. Lipoprotein abnormalities classified according to Fredrickson *et al.* (1967).

	Occlusion	Extreme-1	Representative sample from the material	Extreme-10
	n=7 ¹	n=33	n=70	n=34
	n	n	n	n
Type II	1	1	1	0
Type IV	2	2	1	0
Elevated pre-beta (not classified)	1	2	3	1
Total ²	4 (57 %)***	5 (15 %)	5 (7 %)	1 (3 %)

¹ Of the 8 subjects with occlusion, only 7 were examined with lipoprotein-electrophoresis.

² Type I, III and V were not found.

*** = p < 0.001 compared with a representative sample from the material.

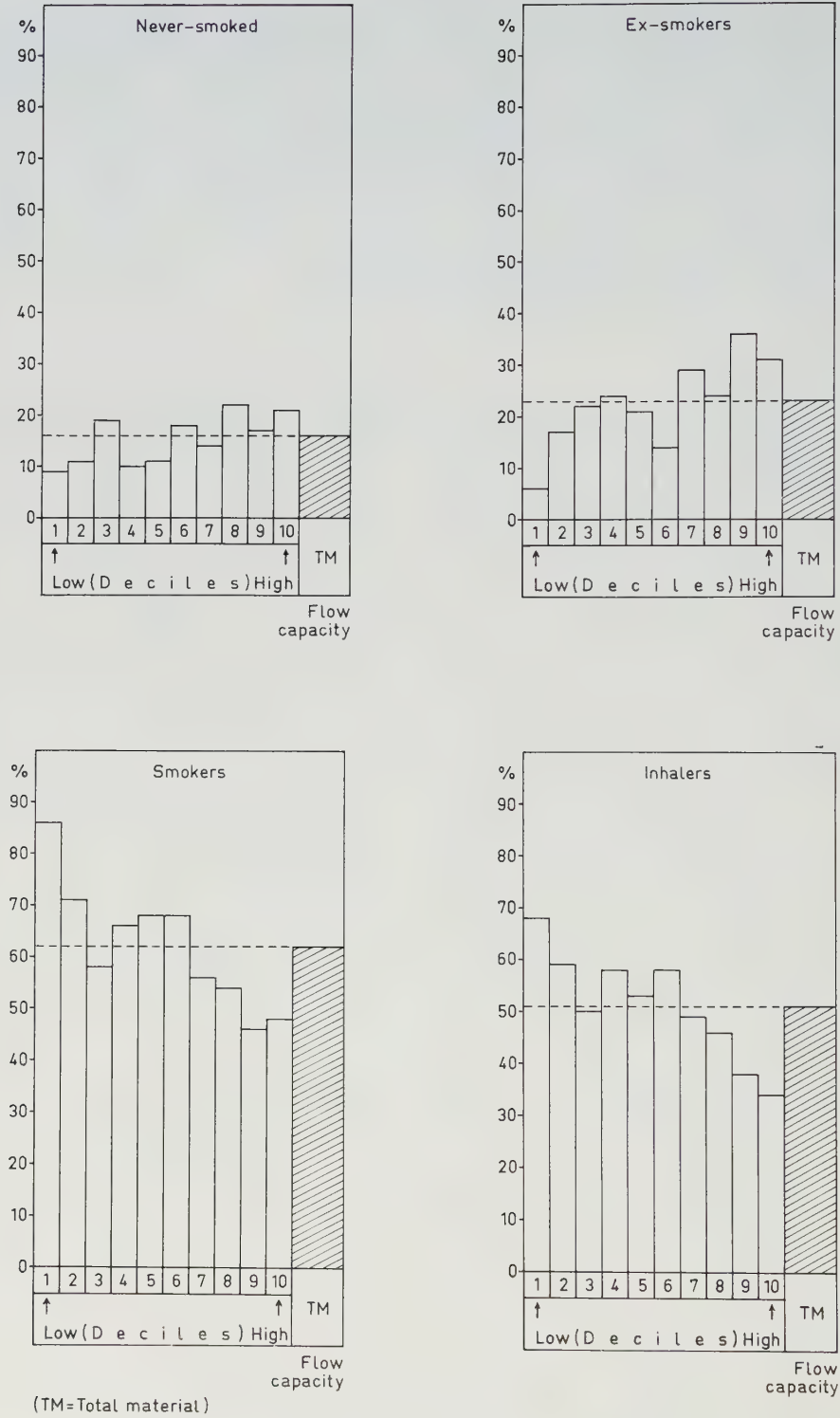


Fig. 2. Smoking habits in flow capacity deciles and in the total material.

significantly greater than in the total material ($p < 0.001$), and in deciles 9 and 10 the frequency of smokers was lower than in the total material ($p < 0.05$).

Inhalers were more common in decile 1 than in the total material ($p < 0.05$); in deciles 9 and 10 the frequency of inhalers was lower than in the total material (decile 9: $p < 0.05$, decile 10: $p < 0.01$).

A further analysis of the relation of smoking habits to the magnitude of the flow capacity is presented in the next chapter.

Physical inactivity

a. Occupational activity

The degree of occupational activity was essentially the same among the different deciles. There was no significant difference between the extreme groups of decile 1 and 10, and the total material.

b. Spare-time activity

An analysis of the spare-time physical activity from age 20 to 40 showed that there were no significant differences among the various deciles or between the two extreme groups and the total material. From the age of 40 onwards, there were differences which became more marked during the years just before the population study.

Spare-time physical activity classified as group III during the year before the population study is presented in Figure 3.

Group III physical activity (regular physical activity such as heavy gardening, running, tennis etc.) was more common in the extreme group of decile 10 than in the total material ($p < 0.05$). Such a difference could not be demonstrated between any other group and the material as a whole.

Group IV physical activity was indulged in by very few and there were no obvious differences among the flow-groups.

Group I and II physical activity was approximately equally frequent in the different deciles.

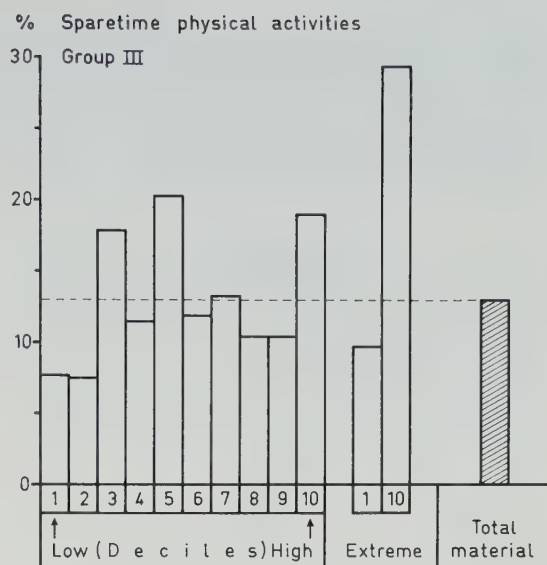


Fig. 3. Prevalence rate of group III spare-time physical activities in flow groups and in the total material.

Weight

The average weight in decile 1 was about 1 kg more than in the total material. There were no significant differences between the single deciles and the total material. No attempt was made to determine the amount of fat in the subjects in connection with the study, and no conclusions can be drawn regarding a possible relation between obesity and flow capacity.

Stress

A rough estimate of the presence of stress in the different subjects was made with the aid of a questionnaire (see chapter 3). No relation could be demonstrated between the presence of stress and the magnitude of the flow capacity.

Hypertension

Systolic and diastolic casual blood pressure in those with documented occlusion in the ilio-femoral arteries has been presented earlier (Table 15). The mean systolic, but not the diastolic blood pressure in these patients was significantly increased compared with that of the total material ($p < 0.001$). The mean blood

pressures among the different deciles were essentially the same, owing to the method used in the calculation of flow capacity. A special analysis of the relation between blood pressure and peripheral circulation is given in chapter 8.

DISCUSSION

An analysis of the risk factors for cardiovascular disease should be viewed in context against the background of how the material was classified. From the author's point of view and with all limitations of measurement in mind, the below described groups were formed:

(1) *Iliofemoral occlusions*. Eight subjects in the material were diagnosed as occlusions or near-total occluding stenosis in the iliofemoral arteries. From the point of view of vascular health, this group was the most severely afflicted.

(2) *Decile 1 and extreme-1*. These comprise the subjects who had the lowest flow capacity. The plethysmographic findings in these subjects correspond to those reported in subjects with angiographically diseased vessels in the absence of occlusion by Dahn (1965) and by Fajgelj *et al.* (1967). Seven subjects with occlusion are found in extreme-1. If they are omitted, a group of subjects with extremely low mean flow capacity but without occlusion results. There was very probably a greater prevalence of arteriosclerosis in group 1 and extreme-1 than in the rest of the material.

(3) *Decile 10 and extreme-10*. These groups comprise subjects with exceptionally high flow capacity for their age. The vascular tree might possibly be healthier in these groups than in the rest of the material.

The applied methods, then, allow a comparison between known risk factors for cardiovascular disease and different degrees of arterial disease.

The diagnosis of intermittent claudication, which is difficult to establish, has not been used as a criterion of arterial insufficiency. The evaluation has in all cases been made with venous occlusion plethysmography, an objective method.

Increased cholesterol and triglyceride concentrations were found only among those with documented occlusion. An elevation of these lipids was not observed in a group of subjects with low flow capacities but without occlusion.

Several authors have found a high triglyceride level to be more common than high cholesterol values in peripheral vascular disease (Carlson and Wahlberg 1966, Greenhalgh *et al.* 1971). Consequently, it is logical to expect hypertriglyceridaemia rather than hypercholesterolaemia to be concomitant with peripheral vascular disease.

Lipoprotein abnormalities were significantly more common in the occlusion group than in a representative sample comprising 10 % of the material.

The lipoprotein patterns in those with angiographically verified peripheral arterial obliteration were studied by Greenhalgh *et al.* (1971). His patients had a mean age of 55 years, and in 39 %, lipoprotein abnormalities were evident.

Lipoprotein electrophoretic examination will probably be of greater diagnostic and prognostic importance than cholesterol and triglyceride determinations in the future (Carlson 1970).

Our own investigations showed that 57 % of the subjects with occlusion in the iliofemoral arteries had lipoprotein abnormalities. This frequency is approximately the same as in a post-infarction material consisting of men below the age of 55 (Boberg and Gustafson 1970). In this latter material, lipoprotein abnormalities were demonstrated in 55 % compared with 22 % prevalence in a control material consisting of 100 randomly selected 55-year-old men.

Consequently, lipoprotein abnormalities seem strongly related to both coronary artery disease (Boberg and Gustafson 1970, Furberg and Dahlén 1971) and peripheral arteriosclerosis (Greenhalgh *et al.* 1971).

Low flow capacity in the absence of occlusion was not related to any demonstrable disturbance in the lipid pattern.

Perhaps the most impressive findings are the relations seen between the magnitude of flow

capacity and various smoking habits. Almost all subjects in decile 1 were smokers, and most of the inhalers are found in this group as well. Decile 9 and 10 had the fewest smokers but the most ex-smokers. These findings render tobacco smoking suspect as one cause of initiating the low flow capacity in the legs. Investigations carried out by Astrup *et al.* (1967) and by Kjeldsen (1969) support the concept that carbon monoxide inhaled with tobacco smoke promotes arteriosclerosis. Reports by Hess and Frost (1968) showed that smoking can also be a factor in thrombosis. Autopsy studies carried out by Auerbach *et al.* (1968) identified a significantly increased fibrosis of the walls of the arterioles and small arteries with increased cigarette consumption. It is apparent that smoking could directly cause arterial injuries and thereby be responsible for the observed relation between smoking and reduced flow capacity.

Of those eight cases of occlusion, all were either smokers or ex-smokers. A more thorough analysis regarding the relation between smoking and flow capacity is presented in the following chapter.

The relation between high blood pressure and arteriosclerosis has been studied by many authors; the predominant opinion is that arteriosclerosis and hypertension are different diseases, but that hypertension accelerates the course of arteriosclerosis (Stamler 1962, Sternby 1968, Robertson and Strong 1968). In the present study, a statistical relation has been demonstrated between high systolic blood pressure in the arm and occlusion in the ilio-femoral arteries. This relation is expected as most members of the occlusion group had generalized arteriosclerosis. It is natural for the systolic blood pressure to be high in the presence of a rigid arterial system. The relation between hypertension and peripheral circulation is further discussed in chapter 8.

So far, the relation between low flow capacity and various risk factors have been discussed. What is then significant for the subjects with

the highest flow capacity? The subjects in the extreme-10 group of decile 10 (highest flow capacity) were primarily characterized by more physical activity in their spare-time. Previous investigations have shown that habitual physical inactivity is related to the incidence of coronary artery disease (Simborg 1970). Investigations regarding the relation between physical activity in spare-time and at work, on one hand, and the incidence of myocardial infarction, on the other, have been carried out by Wilhelmsen and Tibblin (1971). They used the same questionnaire as was employed in the present study and found that low physical activity (group I—II) during the last year was significantly more common in those who later had a myocardial infarction than in a randomly selected group of men (53—54 years old).

Concerning the circulation in the legs, a rise in the flows during reactive hyperaemia was observed after physically training subjects with intermittent claudication due to arterial occlusion (Ericsson *et al.* 1971, Fitzgerald *et al.* 1971). This might be because physical training stimulates development of collateral circulation (Eckstein 1957, Sanne and Sivertsson 1968).

However, plethysmographic studies have shown that the blood flow to the musculature of the working extremity is greater in trained than in the untrained subjects (Pernow 1971). Conceivably physical training can induce a more effective distribution of the available blood to the exercising muscles.

The explanation for the relation between high spare-time physical activity and high flow capacity could consequently be healthy vessels and/or possibly altered distribution of available blood during reactive hyperaemia.

The existence of multiple risk factors should also be discussed in this context. Concerning the incidence of coronary artery disease, it is known that the existence of multiple risk factors, as opposed to only one, considerably augments the likelihood of coronary artery disease (Epstein 1965, Simborg 1970, Atherosclerosis study group 1970, Tibblin 1970). The smallness of the group

with occlusion precludes firmness of findings, but we were able to establish that hypertension, hyperlipaemia, and smoking were all present in this group. It is known that the presence of multiple risk factors (over-weight, hyperlipaemia, hypertension, and cigarette smoking) is more common among those with occlusion of the leg arteries than among those with no such disease (Widmer *et al.* 1969).

With the exception of smoking, there was no relation between low flow capacity in the absence of occlusion and the various risk factors. Conditions were somewhat different in regard to subjects with the highest flow capacities. In the extreme group of decile 10, there were a high frequency of subjects physically active in their spare-time, a large number of ex-smokers, and a low number of smokers. Furthermore, the serum triglycerides were lower in this group than in other groups. A subsequent analysis showed that group III spare-time physical activity during the last year was more common among ex-smokers than among those who smoked ($p < 0.01$). However, mean triglyceride concentration of the ex-smokers as a group was not lower than that for the rest of the material. In the extreme group of decile 10, somewhat lower triglyceride values were found for group III physically active subjects than for the rest of the subjects in decile 10. Previous reports illustrate that the serum triglyceride concentration is lower in those who are regularly physically active in their spare-time, but not in those who do heavy physical work (Carlson and Lindstedt 1968). Investigations carried out by Holloszy *et al.* (1964) showed that physical activity effects fat metabolism in such a way that mean serum triglyceride concentration in a mixed material of inactive middle-aged men decreased significantly after each training period and this

persisted for 48 hours. The slightly lower level of triglycerides in the group with the best flows can perhaps be ascribed to the better exercise habits adopted by members of this group. In addition, many members of the extreme group of decile 10 were ex-smokers. At the same time, ex-smokers as a group, were found to be more physically active than smokers.

An analysis of risk factors was performed in yet another way. Cholesterol and triglyceride levels above the median, more than 14 gm tobacco consumption per day, and group I and II physical activity were considered risk factors. The number of subjects with one or more such risk factors was calculated for each decile. Except that the number of heavy smokers was greatest in decile 1, there were no essential differences among the deciles in terms of this analysis.

SUMMARY

In 55-year-old men, it was found that systolic hypertension, hypercholesterolaemia, hypertriglyceridaemia and lipoprotein abnormalities were clearly related to occlusive vascular disease in the iliofemoral arteries. Smoking proved to be clearly related to the magnitude of the arterial flow capacity in the legs and also to occlusive vascular disease. Smoking may have the ability of generally influencing the whole arterial tree. Physical inactivity, occupational or spare-time, was not related to low flow capacity, but high physical activity in spare-time was correlated to extremely high flow capacity in the legs. More subjects with high flow capacity than members of deciles with low flow capacities were ex-smokers. The ex-smokers were more active in their spare-time than the smokers.

7. SMOKING HABITS AND PLETHYSMOGRAPHIC FINDINGS

In recent years, a vast literature has accumulated which overwhelmingly supports the concept of a strong relation between smoking and morbidity and mortality in ischaemic heart disease, lung cancer, chronic bronchitis, emphysema, and other diseases.

A WHO report by Fletcher and Horn (1970) provides a summary of results from earlier published investigations. The large prospective studies have proved clearly that (1) cigarette smokers as a group have 30–80 % higher overall mortality than non-smokers; (2) mortality rises with increasing cigarette consumption; (3) mortality is proportionally higher among cigarette smokers between 45 and 54 years of age than at earlier and later ages; (4) mortality is higher in those who began smoking in earlier years than in those who began later; (5) mortality is higher among inhalers than non-inhalers, and (6) mortality is lower among cigarette smokers who stopped smoking than among those who have continued.

A very strong relation has been shown between

smoking and mortality in ischaemic heart disease, independent of all other risk factors (Morris *et al.* 1966, Truett *et al.* 1967). Other investigations suggest that smoking is related not only to ischaemic heart disease but also to “stroke” (Dawber and Thomas 1969) and to occlusive disease of the arteries of the leg (Widmer *et al.* 1969, Räf 1969, Kjeldsen 1970).

It seems safe to say that a manifest relation exists between smoking and arteriosclerotic disease in different parts of the arterial tree.

The statistical correlation between smoking and flow capacity has been mentioned in the previous chapter. This chapter presents a more detailed analysis of various smoking habits and their relation to the magnitude of the flow capacity.

RESULTS

The reliability of the questionnaire as regards smoking habits proved satisfactory (see chapter 3). Table 20 presents the smoking habits of the total material. Thirty-seven per cent smoked

Table 20. Smoking habits of the subjects (n=703).

Never smoked		Ex-smokers		Smokers				Total tobacco consumption gm/day					
				Non-inhalers		Inhalers		1–14		15–24		≥25	
								n	%	n	%	n	%
n	%	n	%	n	%	n	%	n	%	n	%	n	%
108	(15)	159	(23)	77	(11)	359	(51)	258	(37)	141	(20)	37	(5)

moderately, *i.e.* 1–14 gm/day, and 26 % were considered heavy smokers (15 gm or more/day). All subjects who had ever smoked had, as a group, begun to do so at an average age of 19 years. The ex-smokers had smoked until mean age 43, and therefore had not smoked, on the average, for 12 years before the population study. The smoking habits during their years as active smokers did not differ from those of the subjects who continued to smoke. The tobacco consumption per day had possibly been somewhat higher among the ex-smokers.

Clinical findings and findings derived from the medical histories in relation to the smoking habits

These findings are presented in Table 21. Angina pectoris occurred more frequently in the group composed of inhalers than in those who had never smoked. Intermittent claudication, as indicated by questionnaire was also more common among inhalers than in those who had never smoked.

The almost total lack of these symptoms and diseases among those who had never smoked is remarkable.

Daily consumption of tobacco

The daily consumption of tobacco (cigarettes, pipe-tobacco, cigars, or cigarillos) is reported in Figure 4. The smokers have been identified as either genuine cigarette smokers, genuine pipe-smokers, genuine cigar or cigarillo smokers, or

smokers with mixed tobacco consumption habits (combined smokers). Of all these, 42 % were heavy smokers (15 gm or more/day), with genuine cigarette smokers contributing 26 % and with very few genuine pipe or cigar smokers (4 %).

Inhalation

About eighty-five per cent of the genuine cigarette smokers and the pipe-smokers were inhalers. Inhaling occurred somewhat more frequently among the heavy smokers. Sixty-two per cent of the cigar smokers who consumed 1–14 gm daily inhaled as did 50 % of those who used 15–24 gm daily, thus revealing lower frequency of inhaling than did other groups.

Height and weight

Height and weight in relation to smoking habits are reported in Table 22 for the subjects examined with plethysmography.

The greatest mean height was noted in the group whose members smoked 15 gm or more a day.

The least mean weight was noted in the group whose members smoked less than 15 gm/day.

Blood pressure and heart rate

Blood pressure and heart rate are reported in Table 23. Systolic and diastolic arm blood

Table 21. Medical history and arteriosclerotic diseases in relation to smoking habits.

	Myocardial infarction		Angina pectoris (questionnaire)		Occlusion		Intermittent claudication (questionnaire)	
	n	%	n	%	n	%	n	%
Never smoked n=108	0		2	(1.9)	0		0	
Ex-smokers n=159	3	(1.9)	9	(5.7)	2	(1.3)	4	(2.5)
Smokers: non-inhalers n=77	0		3	(3.9)	0		1	(1.3)
„ inhalers n=359	7	(2.0)	28*	(7.8)	6	(1.7)	15*	(4.2)

*=0.01 < p < 0.05, compared with those who had never smoked.

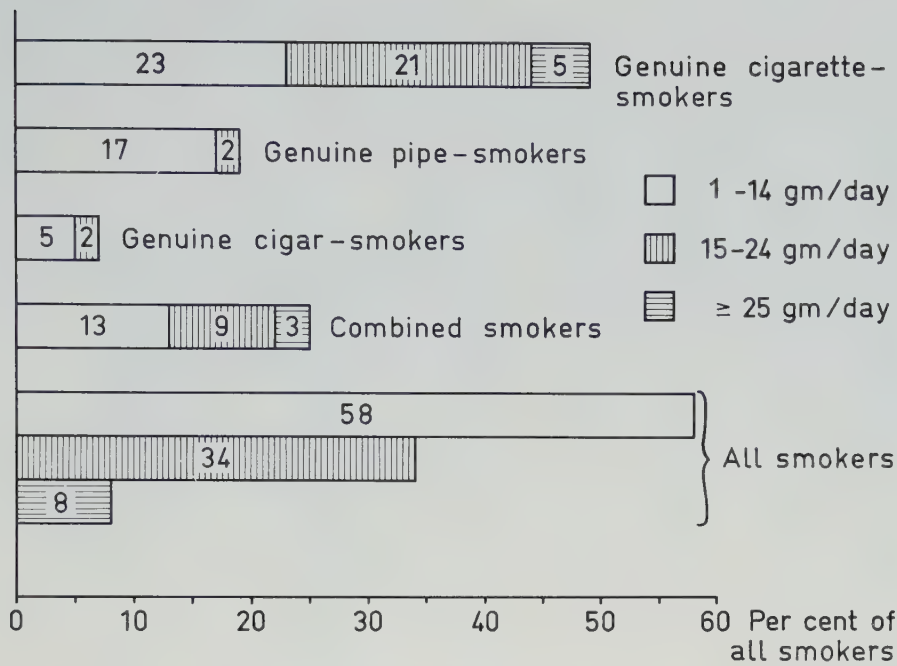


Fig. 4. Smoking habits among the 436 smokers in the material. Combined smokers are those who smoked combinations of cigarettes and/or pipe and/or cigars.

Table 22. Height and weight related to smoking habits of those examined plethysmographically.

	n		Height	Weight
Never smoked	104	m	174.0	76.1
		SD	7.5	10.5
Ex-smokers	155	m	174.5	76.9
		SD	6.5	10.5
Smokers:				
Totally <15 gm/day	249	m	174.8	73.7*
		SD	6.0	11.1
Totally ≥15 gm/day	176	m	176.0**	74.7
		SD	6.0	10.6

* =0.01 < p < 0.05.
** =0.001 < p < 0.01 compared with those who had never smoked.

pressures were significantly lower in the smokers, regardless of daily tobacco consumption. The heart rate was somewhat lower in the smokers than in others.

The ex-smokers did not differ from those who had never smoked in regard to blood pressure and heart rate.

Flow capacity

The magnitude of flow capacity in the legs among those with varied smoking habits is reported in Figures 5, 6, and 7.

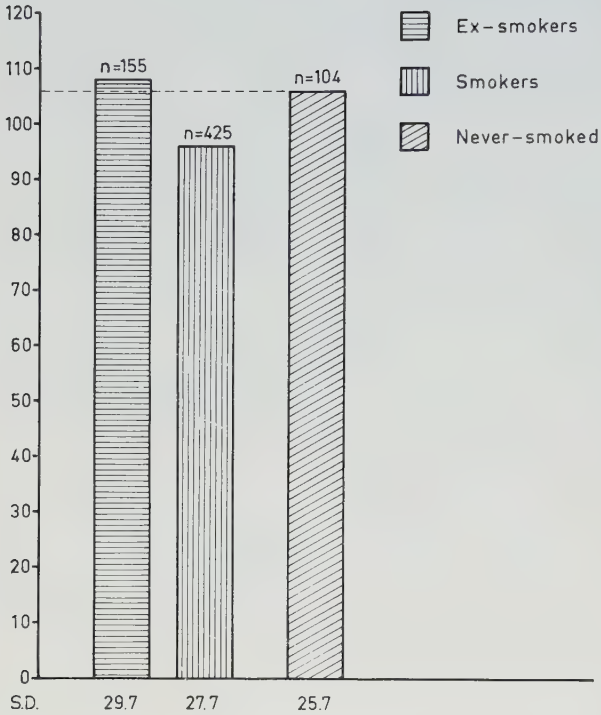
Table 23. Blood pressure and heart rate related to smoking habits of those examined plethysmographically.

		Arm blood pressure		Heart rate	
n		Systolic	Diastolic		
Never smoked	104	m	145	89	69
		SD	22	12	12
Ex-smokers	155	m	144	86	68
		SD	23	15	14
Smokers:					
Totally <15 gm/day	249	m	135***	81***	65*
		SD	20	15	11
Totally ≥15 gm/day	176	m	134***	81***	65*
		SD	22	13	13

* =0.01 < p < 0.05.
** =0.001 < p < 0.01 compared with those who had never smoked.

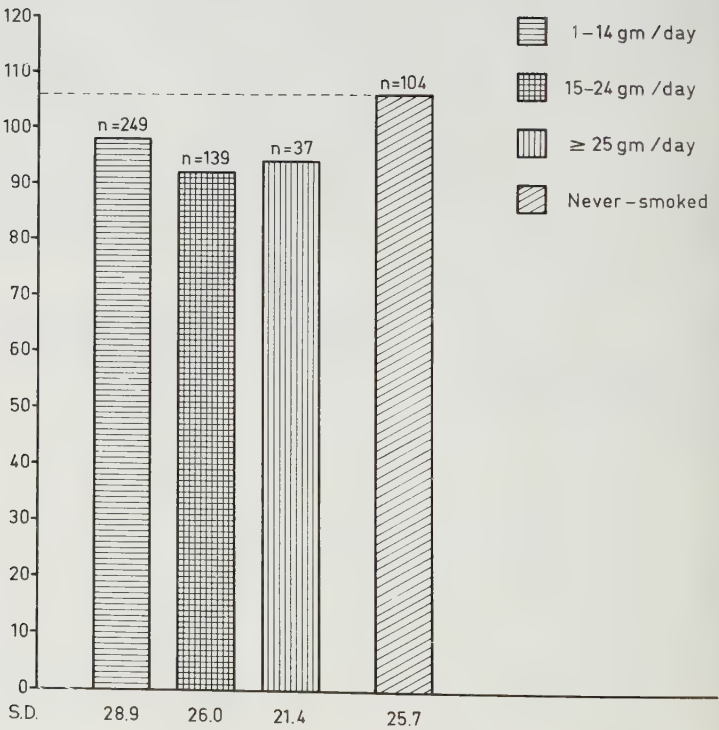
Flow capacity

Fig. 5. Flow capacity in those with varied smoking habits.



Flow capacity

Fig. 6. Flow capacity related to daily tobacco consumption.



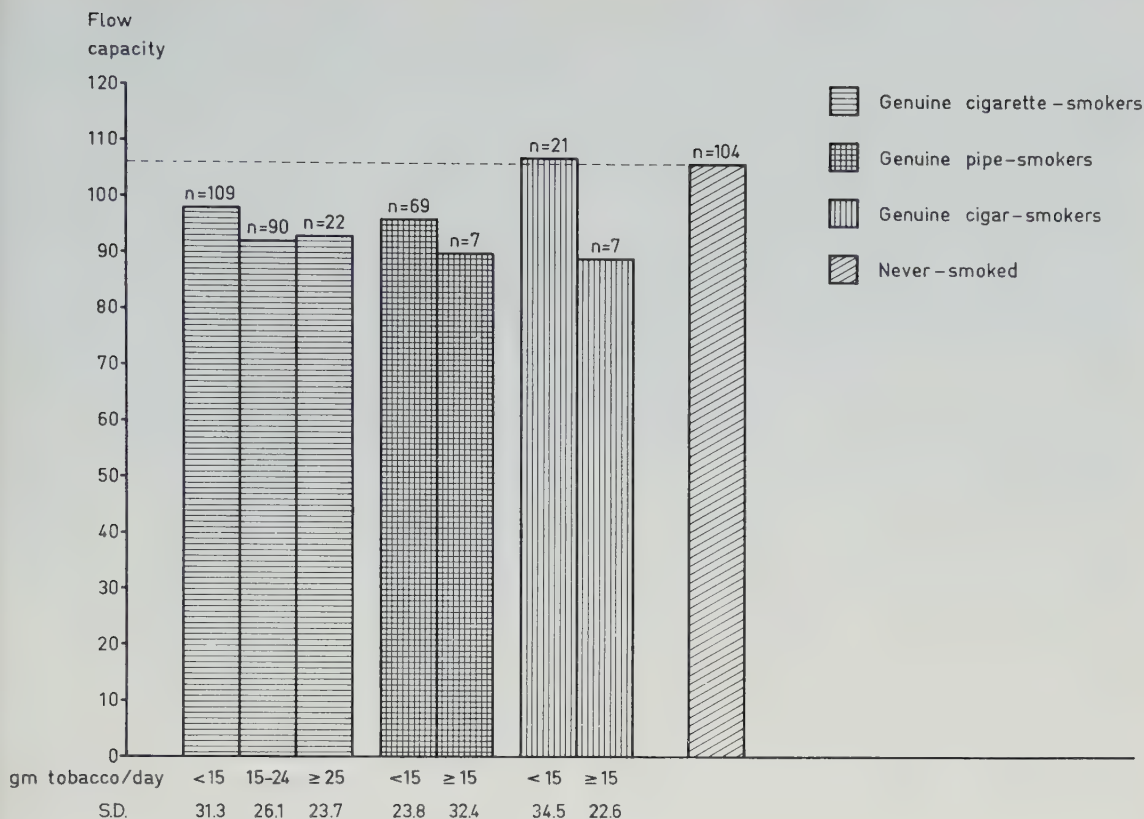


Fig. 7. Tobacco consumption, mode of smoking, and flow capacity.

The smokers had a significantly lower mean flow capacity than did the non-smokers (Figure 5). The mean flow capacity of the inhalers was significantly lower than that of those who had never smoked ($p < 0.001$).

At 1–14 gm tobacco consumption (Figure 6) the flow capacity in the legs was moderately reduced ($p < 0.05$), but at a larger consumption (≥ 15 gm) there was a statistically significant reduction of flow capacity ($p < 0.001$).

Genuine cigarette smokers (Figure 7) had a moderately reduced flow capacity at a daily consumption of 1–14 gm and a significantly reduced ($p < 0.001$) flow capacity when consumption was 15 gm or more.

Cigar smokers consuming 1–14 gm/day had the same flow capacity as those who had never smoked.

The genuine pipe-smokers had a significantly reduced flow capacity in the legs ($p < 0.01$) at a consumption of 1–14 gm/day. The few pipe-smokers ($n=7$) who smoked 15 gm of pipe-tobacco or more/day, showed a further reduction of the flow capacity to approximately the same level as heavy cigar and cigarette smokers.

DISCUSSION

The reliability of the questionnaire concerning smoking habits must be considered acceptable. When the smoking habits of a similar population of 54-year-old men investigated in Gothenburg in 1967 (Tibblin and Wilhelmsen 1970) are compared with the results of the present study, some differences are found; in the Malmö study,

9 % more smokers were reported than in the Gothenburg study.

The effect of smoking on the circulation is essentially a function of the nicotine in tobacco (Armitage 1965, Larson and Silvette 1968) which stimulates the release of adrenaline and nor-adrenaline from the adrenals.

The temporary effect of smoking or otherwise taking nicotine can consequently be ascribed to a sympathetic response involving catecholamine secretion and increased heart rate, the rise in both systolic and diastolic blood pressure, vasoconstriction of the skin, and vasodilatation in muscles (Shepherd 1963).

However, several authors have found that the blood pressure measured when the subject was not smoking was lower in smokers (Lundman 1966, Blackburn *et al.* 1960) than in non-smokers. Lundman believed this to be due to the period without smoking just before blood pressure measurement. Consequently, the non-smokers ought to have a slightly higher blood pressure than the smokers. Tibblin (1967), whose population was divided into blood pressure groups, found more non-smokers in the groups with high blood pressure than in the low-pressure groups. It was postulated that obesity in non-smokers might account for this phenomenon. But Keys *et al.* (1967) found that, when they ignored obesity, there was still an excessive frequency of subjects with high blood pressure among non-smokers and they concluded that body fatness was not the explanation for their findings.

In the present study, the amount of body fat was not determined. The smokers were slightly lighter than the non-smokers. But the depressed systolic and diastolic blood pressures in the smokers were so marked as to suggest that factors other than weight may have been involved. The blood pressure of the examined smokers was determined after about 7 hours without tobacco. It is possible that the lower blood pressure and heart rate in the smokers could be the result of unknown mechanisms related to this period of abstinence, perhaps

central-nervous system oriented, such as a central blocking of the intracerebral reflex which can persist for as long as 12 hours after the use of nicotine (Tibblin 1970). Another explanation could be a temporary adrenal insufficiency, which has been considered possible after the initiation of smoking abstinence (Arvidsson 1971).

The discussion of the relation between smoking, blood pressure, and heart rate is important for the interpretation of the present results. Both blood pressure and pulse rate affected the magnitude of the first flow during reactive hyperaemia. The calculation of flow capacity, however, suggested that the influence of these variables, and also that of height, was eliminated. No anthropometric or physiological variable explaining the reduced flow in the smokers has been found.

Morphological arterial changes might explain the reduced flow capacity in smokers. The flow capacity was based on the first measured flow during reactive hyperaemia. It has previously been shown that this method results in a sub-maximum vasodilation (Shepherd 1963, Bollinger 1969). Flow would then be conditioned by changes limiting the dilating capacity of the arterial tree. Examinations carried out by Auerbach *et al.* (1968) showed that cigarette smokers had a significantly increased fibrosis of the arterial walls compared with non-smokers and that fibrosis was most evident among heavy smokers.

Kjeldsen (1970) believed that the higher frequency of arteriosclerotic disease in smokers was due to a markedly greater concentration of carbon monoxide in the blood. Tobacco smoke contains much carbon monoxide. A loss of up to 10 % of the capacity of the blood to transport oxygen can thus occur in smokers (Goldsmith and Landaw 1968). Exposure to carbon monoxide causes an increased formation of atheroma in experimental animals. Similar effects in man could explain the increased risk for smokers to develop arteriosclerotic heart and vascular diseases (Astrup *et al.* 1967, Kjeldsen 1969).

Furthermore, certain investigations indicate that smoking is of importance for the aetiology of thrombosis (Hess and Frost 1968, Dalderup *et al.* 1970).

Pipe and cigar smoking, as distinct from cigarette smoking, have not been identified as risk factors for cardiovascular disease, although some investigations have shown that cigar and pipe-smokers who consume larger amounts of tobacco daily and who inhale are basically exposed to the same risk as heavy cigarette smokers (Hammond 1966, Fletcher and Horn 1970). The total tobacco consumption per day appears to be of prime importance.

SUMMARY

Of the examined population of 55-year-old men, 62 % were smokers. When compared with those who had never smoked it was found that the average smoker was somewhat taller and lighter than his non-smoking counterpart. Mean blood pressure and mean heart rate were lower in the smokers. The arterial flow capacity in the legs was reduced in direct proportion to tobacco consumption per day; this was true regardless of the mode of smoking.

The significantly reduced flow capacity in the smokers is probably due to morphological arterial changes caused by smoking.

8. CALF BLOOD FLOW AND PERIPHERAL RESISTANCE AT DIFFERENT LEVELS OF BLOOD PRESSURE

The magnitude of the arterial blood pressure is determined primarily by two factors, the cardiac output (systemic blood flow) and the resistance to blood flow (total peripheral resistance).

The common opinion held earlier was that the primary disturbance in essential hypertension is an increased peripheral resistance (Werkö and Lagerlöf 1949, Varnauskas 1955, Freis 1960, Horrobin 1966). In recent years, however, there have been indications that a large number of patients with early hypertension of the essential type are characterized by an increased cardiac output at rest and normal peripheral resistance. This has been termed *hyperkinetic circulation* (Bello *et al.* 1965, Finkielman *et al.* 1965, Lund-Johansen 1967, Sannerstedt 1969).

Some investigators state that hypertension with increased peripheral resistance can be explained by a pressure-induced adaptive morphological change in the resistance vessels, whereas the vasomotor tonus remains within normal limits (Folkow *et al.* 1958, Conway 1960, Sivertsson 1970).

This alteration of the resistance vessels has not been classified as arteriosclerosis but is considered to be a hypertrophy of the arterial walls.

The report in this chapter consists of primary data gathered in connection with the population study. A more complete account of a therapeutically planned 1-year study comprising specific members of the population will be presented later in separate articles.

The purpose of this chapter is to elucidate the following problems:

- (1) Is high blood pressure in 55-year-old males associated with hyperkinetic circulation?
- (2) What circulatory changes can be seen in subjects undergoing treatment for hypertension?
- (3) How can the peripheral resistance to blood flow in the calf at rest and during reactive hyperaemia at various levels of systolic and diastolic blood pressure be characterized?

Special methodology

In order to estimate the importance of the level of blood pressure in the studied population, a special group-assignment has been arranged as follows (Figure 8):

I. $\geq 165/\geq 110$. This group is composed of subjects with systolic blood pressure of ≥ 165 mm Hg and a simultaneous diastolic blood pressure of ≥ 110 mm Hg. None received treatment for hypertension at the time of the study. This group is comprised of 5 % of the material (n=34).

II. *Systolic hypertension*. This group is comprised of the 5 % of the material with the highest systolic blood pressure (n=34).

III. *Diastolic hypertension*. The 5 % with the highest diastolic blood pressure are found here (n=34).

IV. *Systolic hypotension*. The 5 % of the material with the lowest systolic blood pressure were assigned to this group (n=34).

V. *Diastolic hypotension*. The 5 % with the

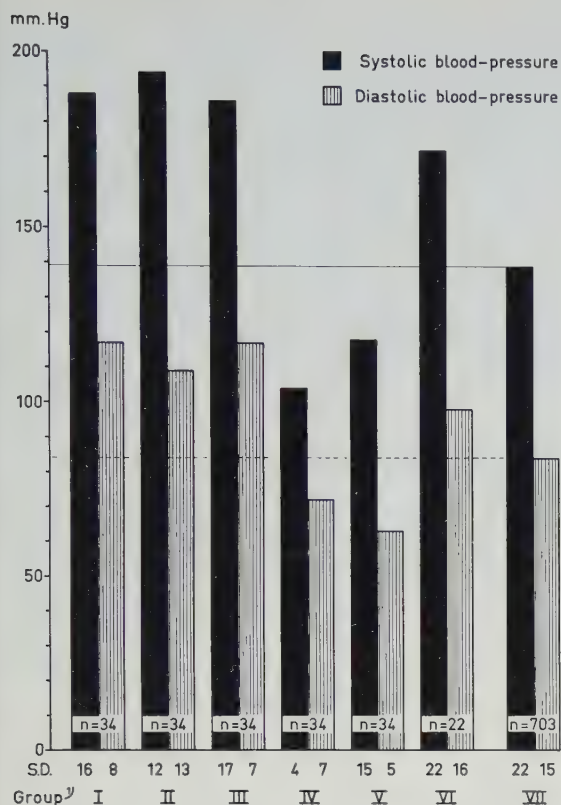


Fig. 8. Resting mean arterial blood pressure in the blood pressure groups.

¹ Group structure described on page 50–51.

lowest diastolic blood pressure are in this group ($n=34$).

VI. *Treated*. This group includes individuals subjected to more or less active blood pressure treatment. Subjects taking digitalis were excluded ($n=22$).

VII. *The total material* ($n=703$). Of these, 684 had been examined with plethysmography.

Overlapping occurred between some groups. Between group I and VI there was no overlapping. Group III is essentially identical with group I except for 4 subjects. Twenty-one of the 34 subjects in group II are also included in group I. Ten subjects belong to both group IV and V.

Blood pressure treatment was not given to any subject in group I, IV and V. Treatment

was given to 4 subjects in group II and to two subjects in group III.

The casual sitting blood pressure was determined as previously described. The heart rate at rest was determined with ECG.

As the material was grouped on the basis of blood pressure, the flow capacity has not been reported, the influence of the blood pressure on the flow being eliminated in the calculation of the predicted flow (see chapter 4). The peripheral resistance has been calculated instead, based on the arm blood pressure measured at plethysmography, blood flow at rest, and reactive blood flow of the calf.

The quotient between the mean blood pressure of the arm and the calf blood flow has been reported in *Arbitrary Units* in the same way as described by other authors (Folkow *et al.* 1958, Conway 1960, Sivertsson 1970).

Statistical comparisons have been made between single groups and the total material throughout.

RESULTS

Height and weight

Anthropometric data are presented in Table 24. All groups with high blood pressure had somewhat higher mean weight than that of the total material ($p<0.05$). The group with *diastolic hypotension* weighed significantly less ($p<0.001$). The height was essentially the same in all groups, except the group *systolic hypotension*, where the subjects were somewhat taller ($p<0.05$). Greater weight than, but about the same height as, other groups characterized the hypertension groups.

Heart rate at rest

The heart rate at rest is reported in Figure 9. All groups with high blood pressure had higher mean resting heart rate than did the total material. This rise was most pronounced in the *diastolic hypertension* group ($p<0.001$).

The hypotensive groups had somewhat lower mean heart rate at rest than did the total material.

Table 24. Anthropometric data of different blood pressure groups.

Group	I	II	III	IV	V	VI	VII
	$\geq 165/\geq 110$	Systolic hypertension	Diastolic hypertension	Systolic hypotension	Diastolic hypotension	Treated	Total material
n	34	34	34	34	34	22	703
Height m	174	174	174	177*	174.5	174	175
SD	8	8	7	6	7	6	7
Weight m	79*	79*	79*	72	69***	79*	75
SD	13	13	12	12	10	13	11

*=0.01 < p < 0.05, ***=p < 0.001 compared with the total material.

Rate/min.

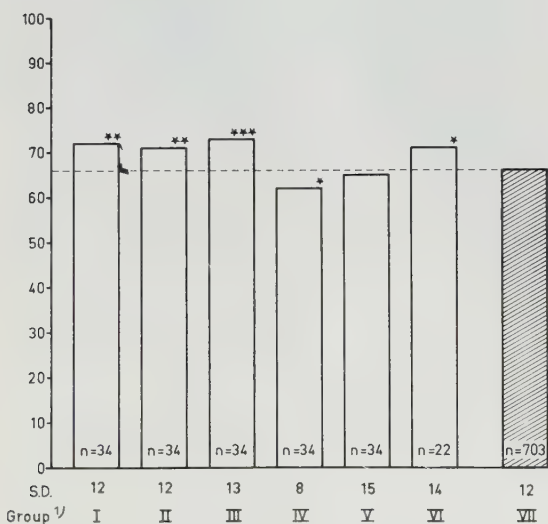


Fig. 9. Heart rate at rest in the blood pressure groups.

¹ Group structure described on page 50–51.

*=0.01 < p < 0.05, **=0.001 < p < 0.01, ***=p < 0.001, compared with the total material.

Calf blood flow at rest

Calf blood flow at rest, or rest flow, is presented in Figure 10. The mean rest flow was significantly higher in all hypertension groups, except the group *diastolic hypertension*, where the mean rise was moderate. With *systolic hypotension* there was a significantly reduced mean rest flow, whereas the group *diastolic hypotension* had a rest flow about equal to the mean of the total material. The highest mean blood flow at rest was observed in the treated group.

Flow resistance at rest

The flow resistance at rest, *i.e.* the quotient of mean blood pressure at plethysmography and calf blood flow at rest, is presented in Figure 11. The mean rest flow resistance was increased in all hypertension groups, except the treated group. Most of these latter subjects were treated with thiazides.

Reactive calf blood flow

The reactive calf blood flow is presented in Figure 12. Both first flow and peak flow after

mL/min

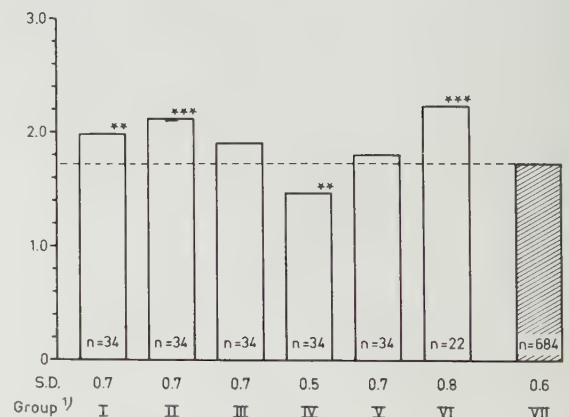


Fig. 10. Rest flow in the calf according to blood pressure groups.

¹ Group structure described on page 50–51.

*=0.01 < p < 0.05, **=0.001 < p < 0.01, ***=p < 0.001, compared with the total material.

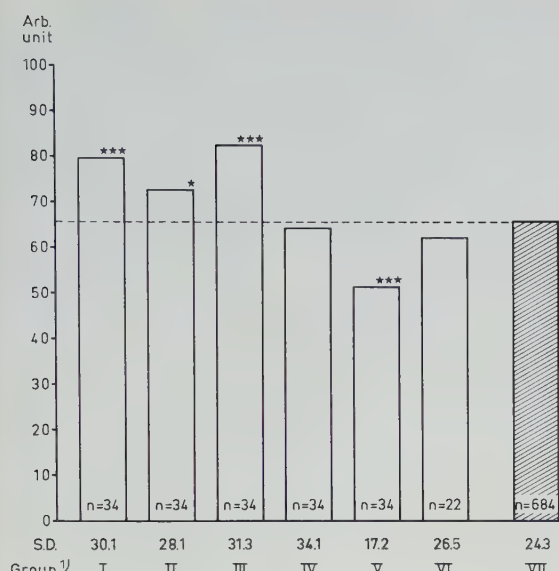


Fig. 11. Resistance to blood flow at rest in the calf according to blood pressure groups.

¹ Group structure described on page 50–51.

*=0.01 < p < 0.05, **=0.001 < p < 0.01, ***=p < 0.001, compared with the total material.

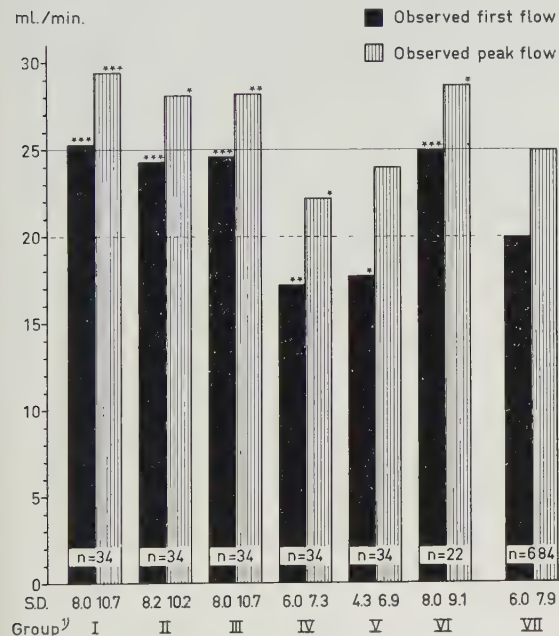


Fig. 12. Observed first and peak flow in the calf according to blood pressure groups.

¹ Group structure is described on page 50–51.

*=0.01 < p < 0.05, **=0.001 < p < 0.01, ***=p < 0.001, compared with the total material.

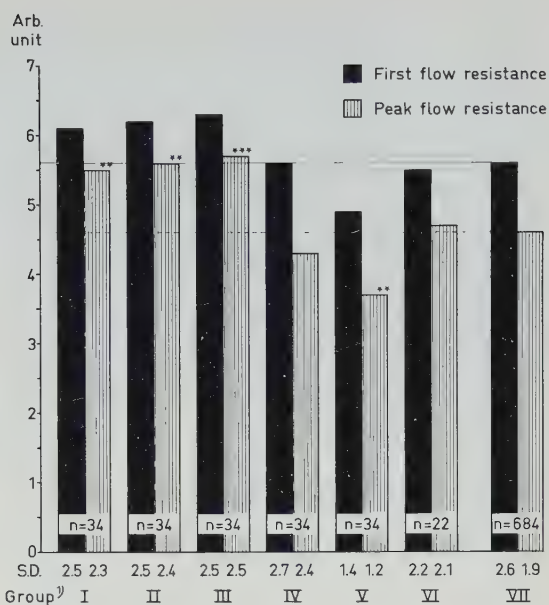


Fig. 13. Resistance to first and peak flow in the calf according to blood pressure groups.

¹ Group structure is described on page 50–51.

*=0.01 < p < 0.05, **=0.001 < p < 0.01, ***=p < 0.001, compared with the total material.

3 minutes of arterial occlusion varied with the level of the blood pressure. The mean first flow was significantly elevated in all the hypertension groups, significantly lower in *systolic hypotension*, and moderately decreased in the *diastolic hypotension* group. The peak flow behaved as the first flow, although the differences were not quite so pronounced.

Reactive flow resistance

Reactive flow resistance, *i.e.* the quotient of mean blood pressure at plethysmography and first flow and peak flow after 3 minutes of arterial occlusion, is reported in Figure 13.

Mean first flow resistance was moderately increased in the hypertension groups, but not significantly so. There was a significantly increased peak flow resistance in all the hypertension groups, except the treated group, where no increase in resistance was observed.

DISCUSSION

The previous opinion that a primary disturbance in essential hypertension is an increase of the peripheral resistance has recently had to give way to the now clear fact that in many cases there is a normal peripheral resistance but elevated cardiac output. Such a hyperkinetic circulation has primarily been considered characteristic of labile hypertension (Finkelman *et al.* 1965, Frohlich *et al.* 1969). However, in Sannerstedt's material (1969), hyperkinetic circulation was seen in early uncomplicated hypertension with the influence of age, sex, and physique statistically accounted for. In well-established essential hypertension and in hypertension of non-essential nature, however, it seems clear that there is in most cases an increase of the peripheral resistance while the cardiac output is usually normal or in advanced cases even reduced (Pickering 1968, Frohlich *et al.* 1969, Sannerstedt 1970).

Hyperkinetic circulation has been considered to exist mainly in young hypertensive individuals, whereas hypertensives over the age of 50 would show a normal or reduced cardiac output and an increased peripheral resistance (Lund-Johansen 1967). Investigations carried out by Amery *et al.* (1967) seem to indicate that exercise induced cardiac output decreases as age increases. According to Strandell (1964) a decrease of cardiac output with increasing age should be present also at rest. Theoretically, the cardiac output would decrease with increasing age and with hypertension; thus, we could expect an especially manifest reduction of cardiac output in older subjects with hypertension.

In other investigations, a control group comparable to the hypertensive subjects has not generally been used. In the present study, the influence of both age and sex has been eliminated, as all participants were men and, at the time of the investigation, were of the same approximate age. The influence of their physique was not eliminated before group-assignment. The group-assignment has been made only on

the basis of arbitrarily selected "cut-off points" in order to obtain sufficiently large groups with similar blood pressure characteristics. The advantage of this procedure is that it is legitimate to use the mean of the total material as a "normal" value. In the case of the group-assignment used, only constitutional factors could be reasonably expected to influence the obtained results. Furthermore, it was found that the weight in the different groups varied, but the height was essentially the same. The plausible explanation for this is that the subjects in the hypertension groups were obese. The problem of differences between directly and indirectly measured blood pressure has been thoroughly discussed, and although opinions may still differ, neither of the methods seems to be markedly influenced by an increased amount of body fat (for literature, see Tibblin 1967). The relation between obesity and blood pressure could thereby appear to be a result of a genuine influence of obesity on blood pressure and not merely of errors of measurement evolving from larger arm circumferences (Tibblin 1967). Therefore the influence of weight on blood pressure has not been eliminated at the calculations.

A comparison of single groups with the total material showed a higher mean heart rate in all groups comprised of subjects with hypertension, not excluding individual deviations. Several authors have shown that higher heart rate is the most constant finding in hyperkinetic circulation with hypertension (Widimský *et al.* 1958, Sannerstedt 1966, Lund-Johansen 1967, Sannerstedt 1969), whereas the stroke volume is normal. The results from the present study indicate that 55-year-old men with hypertension probably had hyperkinetic circulation. Both higher heart rate and higher calf circulation support hyperkinetic circulation in the hypertension groups. This increased circulation could be a regional phenomenon. Investigations by Brod *et al.* (1962) indicate that the blood flow of the skeletal muscle is increased where there is hypertension, whereas Pickering (1936) failed to find any such increase.

The results of this study therefore indicate the existence of hyperkinetic circulation with hypertension at a relatively advanced age. These characteristics are obviously not restricted to the young hypertension patients as was postulated by Lund-Johansen (1967). This author established a low minute volume in hypertensive men above 55 years of age, which might be because no comparison was made with age-matched controls.

Hyperkinetic circulation in the hypertension groups was associated with an increased rest flow resistance. This was evident in all the hypertension groups, except that composed of treated patients. This elevated mean rest flow resistance is not necessarily due to a relatively small peripheral vascular cross-section at rest, but might, instead, represent an inability for hypertensive subjects to sufficiently dilate their vascular beds. This would elevate the quotient of mean blood pressure and rest flow which, by definition, produces an increased peripheral resistance (Sannerstedt 1969). The fact that the treated group did not show an elevated rest flow resistance suggests that despite the effects of the disease, the peripheral vascular bed in hypertensive patients will respond favourably to vasodilating stimuli.

The flows and flow resistances during reactive hyperaemia partly illustrate the response of the peripheral vascular bed to a relatively strong vasodilating stimulus. The increase in the flow during reactive hyperaemia was approximately the same among the various groups. The reaction of the vascular bed in the groups with low and high pressure was similar. Furthermore, it was noted that the flow resistance during maximum dilation, *i.e.* the peak flow resistance, was raised in the hypertension groups in a manner analogous to that of the rest flow resistance. The quotient of rest flow resistance and peak flow resistance was essentially the same in the various

groups. This indicates the existence of a condition that could not be overcome by the dilating effect of 3 minutes of arterial occlusion. Underlying mechanisms might be the unsatisfactory effect of the occlusion and/or morphological arterial changes, which in turn could be the effects of adaptive alterations, as described by several other authors (Folkow *et al.* 1958, Conway 1963, Sivertsson 1970).

The stability of hypertension in the hypertension group is a pertinent question for future discussion. But it should be mentioned that the group with systolic blood pressure of ≥ 165 mm Hg and diastolic blood pressure of ≥ 110 mm Hg, and also a randomly selected control group of the same number, were examined regularly for blood pressure during the course of a year. It was observed that the blood pressure was surprisingly constant at repeated measurements before the initiation of treatment.

SUMMARY

In untreated hypertensive 55-year-old men, the circulation was found to be hyperkinetic. The resting heart rate and the calf blood flow at rest were significantly higher in hypertensive groups than in hypotensive groups. The peripheral resistance to blood flow in the calf at rest was elevated in hypertensive groups, suggesting that the increased rest flow was not compensated for by a physiological dilation of the peripheral vascular bed. This is thought to be due to morphological arterial changes, because a raised resistance was also observed during vasodilation.

Subjects undergoing treatment for high blood pressure had an elevated calf blood flow at rest and an increased heart rate. The treatment had evidently caused a peripheral vasodilation but the heart rate was still high. Treatment of hypertension does not appear to have affected the hyperkinetic component.

SUMMARY

Venous occlusion plethysmography was used to measure the arterial calf blood flow in a defined population of 55-year old men. The objectives were:

(1) to evaluate the utility of venous occlusion plethysmography as a method of epidemiologic investigation;

(2) to validate the diagnosis of intermittent claudication established with a cardiovascular questionnaire recommended by WHO;

(3) to compare the results of venous occlusion plethysmography with other data gathered in connection with the population study (medical history, clinical findings, laboratory data).

Full participation was obtained from 703 (87 %) of 809 randomly selected men born in 1914 and residing in Malmö, Sweden, at the time of the study.

Limited participation by 64 of 106 men who did not appear at the examinations was obtained by home visits, telephone interviews, letter questionnaires, and hospital dossiers.

Very limited or no information was obtained about 42 subjects.

The study began in January 1969 and terminated in January 1970.

The first flow during reactive hyperaemia was considered the variable best discriminating between subjects with healthy and those with diseased vessels.

Significant positive correlation was demonstrated between the first flow during reactive

hyperaemia and arm blood pressure and between the first flow and pulse rate.

Significant negative correlation was demonstrated between first flow and standing height.

The influence of blood pressures, pulse rate, and standing height on the first flow was mathematically accounted for, and for every subject, an index was calculated. This index ($\frac{\text{observed first flow}}{\text{predicted first flow}} \times 100$) has been called

flow capacity in this report. Group assignment has been based on flow capacity.

The flow capacity is considered an adequate measure of the reserve function of the arteries in the legs, thereby indirectly reflecting the possible existence of arterial disease.

According to the WHO questionnaire, intermittent claudication was present in 20 subjects (2.8 %). Arterial flow insufficiency could be demonstrated in only 6 of these subjects at a more thorough examination.

On the basis of plethysmographic findings, occlusion or near occluding stenosis in the ilio-femoral arteries was judged to exist in 8 subjects (1.1 %). The diagnosis was verified angiographically in 7 subjects, and in one subject at autopsy. Five of these 8 subjects had intermittent claudication according to the questionnaire; three had not, because of concurrent diseases which limited their ability to walk.

Four of the 8 subjects with obliterating ilio-femoral artery disease had suffered at least one myocardial infarction; two of these four had

also suffered cerebrovascular disease (stroke).

Hypertriglyceridaemia, hypercholesterolaemia, lipoprotein abnormalities, and systolic hypertension were clearly related to occlusive disease in the iliofemoral arteries; no correlation was demonstrated between these variables and the magnitude of the flow capacity in the absence of occlusion.

High arterial flow capacity in the legs was related to high, regular, spare-time physical activity. High, regular, spare-time physical activity was significantly more common among ex-smokers than among smokers.

The flow capacity in the legs was reduced in direct proportion to tobacco consumption per day; this was true regardless of the mode of smoking.

In groups with high blood pressure, the circulation was found to be hyperkinetic; heart rate at rest and calf blood flow at rest being significantly higher than in the total material.

The peripheral resistance to blood flow in the calf at rest was elevated in groups with high blood pressure, suggesting that the increased rest flow was not compensated for by a physiological dilation of the peripheral vascular bed. This is thought to be due to morphological arterial changes, as an increased resistance was observed also during vasodilation (reactive hyperaemia).

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